FACULTAD DE CIENCIAS

DEPARTAMENTO DE QUÍMICA ORGÁNICA

CONVERGENT APPROACH TO THE SYNTHESIS OF MYRIAPORONE 4 AND DERIVATIVES

MEMORIA que para optar al grado de

DOCTORA EN QUÍMICA

presenta

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“La ilusión despierta el empeño y solamente la paciencia lo termina”

Anónimo

A mis padres

Esta Tesis Doctoral ha sido realizada en el Departamento de Química Orgánica de la Universidad Autónoma de Madrid, en el Institut Català d'Investigació Química (ICIQ) de Tarragona y en el departamento de I+D de PharmaMar en Madrid, bajo la dirección del Prof. Antonio M. Echavarren, a quien quiero agradecer su dedicación, sus enseñanzas y el haberme transmitido la importancia del rigor en el trabajo.

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Esta memoria de Tesis Doctoral consta de una parte que incluye una introducción general de los temas principales, un apartado de resultados y una parte experimental.

El trabajo es fruto de una colaboración con PharmaMar y está encaminado a la síntesis convergente del producto natural myriaporone 4, así como a la síntesis de nuevos derivados bioactivos.

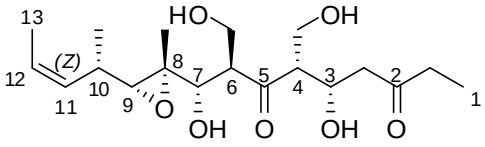
Para hacer que las comparaciones entre las estructuras de myriaporone 4 y de tedanolide sean más claras, los números de los átomos de carbono de myriaporone 4 y sus análogos se han asignado como los del tedanolide.

RESUMEN

En el transcurso de los últimos veinte años el mar se ha convertido en la principal fuente natural de moléculas bioactivas. Esto no es sorprendente si se tiene en cuenta que representa el 70 % de la superficie terrestre y su biodiversidad, el 90 % de la biosfera. Además, estadísticamente, los compuestos de origen marino son más activos que los de origen terrestre ya que el 1.8 % de los productos activos aislados son marinos frente al 0.4 % que representan los de origen terrestre.[1]

En las últimas tres décadas se han registrado cerca de 300 patentes de productos naturales bioactivos de origen marino. El número de productos aislados de varios organismos marinos sobrepasan los 10000, y cada año se descubren cientos de productos nuevos.

Myriapora Truncata es un briozoo aislado en el Mar Mediterráneo. En 1995, Reinehart, aisló cuatro compuestos activos a los que denominó miriaporona, entre los cuales se encontraba la miriaporona 4 (**1**) (Figura 1)[2]. La configuración fue determinada por síntesis total casi simultánemante por PharmaMar[3] y Taylor.[4] Esta molécula de tan sólo trece carbonos está muy funcionarizada. En su estructura cabe destacar un anillo de oxirano, una olefina de configuración *Z*, cuatro grupos hidroxilo y siete estereocentros. Esta molécula presenta una interesante actividad anticancerígena.



1

Figura 1

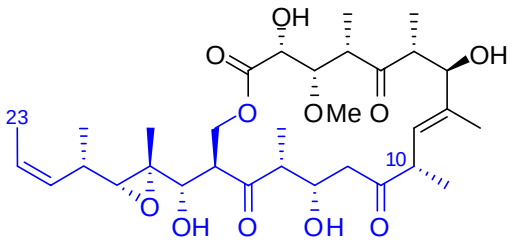
1 (a) Blunt, J. W.; Copp. B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1-49. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1-48. (c) Jiménez, J. C.; Marfil, M.; Francesch, A.; Cuevas, C.; Álvarez, M.; Albericio, F. *Investigación y Ciencia* **2007**, 365-374.

2 (a) Rinehart, K. L.; Cheng, J.-F.; Lee, J.-S. US patent 5,514,708, **1996**. (b) Rinehart, K. L.; Tachibana, K. *J. Nat. Prod.* **1995**, *58*, 344-358.

3 Pérez, M.; del Pozo, C.; Reyes, F.; Rodríguez, A.; Francesch, A.; Echavarren, A. M.; Cuevas, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 1724-1727.

4 (a) Fleming, K. N.; Taylor, R. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1728-1730. (b) Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Org. Lett.* **2002**, *4*, 2953-2955. (c) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361-9364.

La estructura de la miriaporona 4 (**1**) es equivalente al fragmento C10-C23 del macrólido tedanólido (**2**), un potente anticancerígeno aislado previamente de la esponja *Tedania Ignis* (Figura 2).[5] La miriaporona 4 (**1**) es un poco menos activa que el tedanólido **2**, pero el pequeño tamaño de esta molécula y la poca cantidad de que se dispone en la naturaleza, la hacen interesante desde el punto de vista sintético.



2

Figura 2

Recientemente Taylor ha publicado un estudio comparativo de la actividad entre la miriaporona 4 (**1**) y el tedanólido **2** así como la relación estructura-actividad de cada uno de ellos. Llegando a la conclusión, en el caso de **1** de que el anillo de oxirano y los grupos hidroxilo confieren la actividad a la molécula.[6]

Hasta la fecha se han descrito dos síntesis de miriaporona 4 (**1**), la primera fue descrita por PharmaMar[3] y la segunda por Taylor[4]. Ambas están inspiradas en las diferentes síntesis descritas para el fragmento C10-C23 del tedanólido (**2**).[7]

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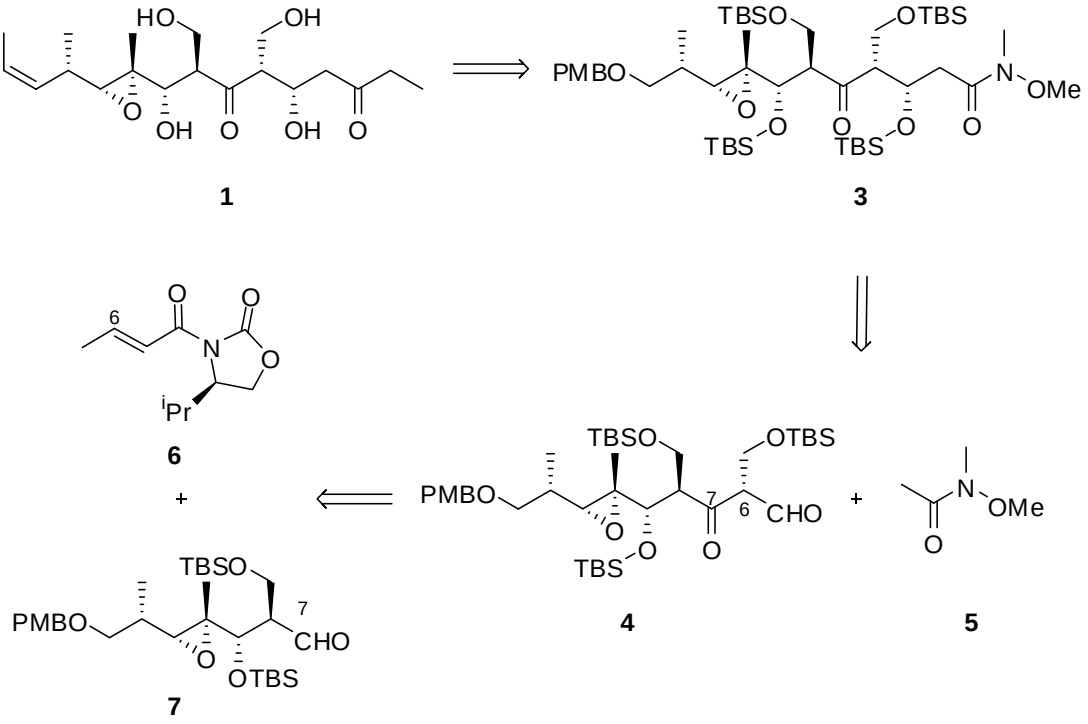
5 (a) Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; Van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251-7252. (b) O'Hagan, D. *Nat. Pod. Reports* **1993**, 593-625.

6 Hines, J.; Roy, M.; Cheng, H.; Agapakis, C. M.; Taylor, R.; Crews, C. M. *Mol. Biosyst.* **2006,** *2*, 371-379.

7 (a) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385. (b) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335. (c) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873. (d) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361. (e) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95. (f) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308. (g) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663. (h) Matsushima, T.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, 780. (i) Smith, A. B., III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249. (j) Zheng, B.-Z.; Maeda, H.; Mori, M.; Kusaka, S.-i.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, J. *Chem. Pharm. Bull.* **1999**, *47*, 1288. (k) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (l)

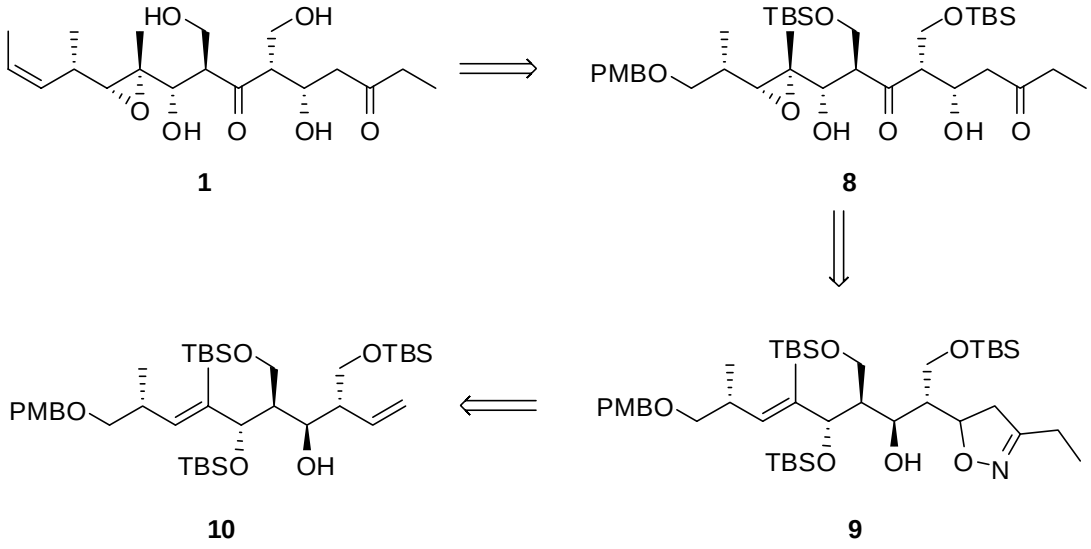
La síntesis de PharmaMar se resume en el siguiente esquema retrosintético (Esquema 1). El resto etilo y el alqueno de configuración *Z* se introducen empleando la amida de Weinreb **3**, la cual se obtiene por reacción aldólica entre el compuesto **4** y la acetamida **5**. Para controlar la estereoselectividad en la formación del enlace C6-C7 entre **5** y **7**, emplean la oxazolidinona de Evans **6** en la reacción aldólica con el aldehído**7**. Para evitar la epimerización y reacciones no deseadas como retroaldólicas o de elminación, la oxidación a cetona del C7 la posponen a los últimos pasos de la síntesis.



Esquema 1

Matsushima, T.; Nakajima, N.; Zheng, B.-Z.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 855. (m) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Kusaka, S.-i.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441. (n) Zheng, B.-Z.; Yamauchi, H.; Dei, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 1761. (o) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (p) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333. (q) Loh, T.-P.; Feng, L.-C.; *Tetrahedron Lett.* **2001**, *42*, 6001. (r) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 3223. (s) Matsui, K.; Zheng, B.-Z.; Kusaka, S.-i.; Kuroda, M.; Yoshimoto, K.; Yamada, H.; Yonemitsu, O. *Eur. J. Org. Chem.* **2001**, 3615. (t) Hearn, B. R.; Ciavarri, J. P.; Taylor, R. E. *Org. Lett.* **2002**, *4*, 2953. (u) Wong, C.-M.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 4485

En la síntesis de Taylor, a diferencia de en la de PharmaMar, el anillo de oxirano se introduce en las etapas finales. La ruta que siguen para la síntesis de **1** está resumida en la retrosíntesis del Esquema 2. Como producto de partida utilizan el intermedio **10** que habían descrito previamente para la síntesis total de otra de las miriaporonas naturales, la miriaporona 1.[4b,c] **10** se transforma en **9** mediante una cicloadición regioselectiva de óxido de nitrilo. Posteriormente se obtiene **8** mediante la oxidación a cetona la posición C7, la reducción de la isoxazolina con $Mo(CO)_6$ y la epoxidación del doble enlace. Finalmente, tras una olefinación para introducir el alqueno de configuración *Z* y la desprotección global se obtiene **1**.

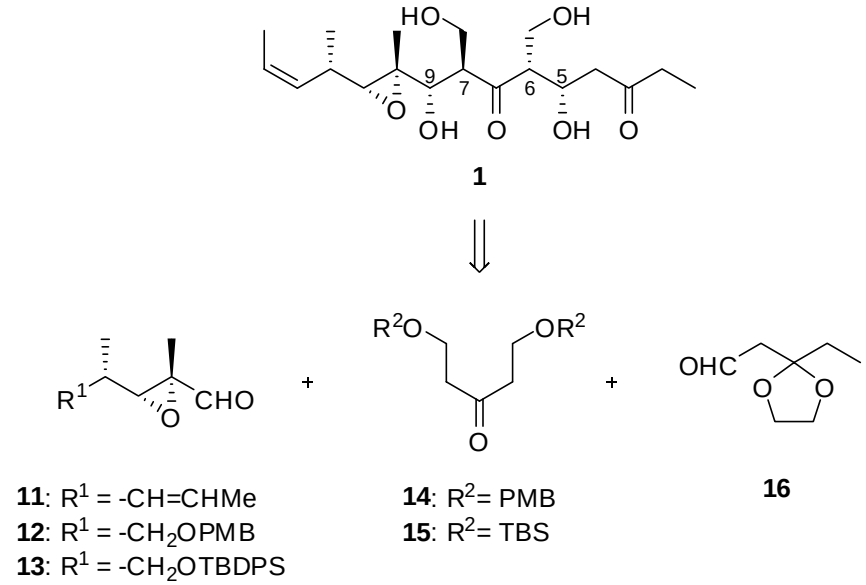


Esquema 2

Ambas síntesis responden a un esquema lineal de síntesis, así pues uno de los objetivos que nos planteamos en este trabajo de investigación es la aproximación convergente a la síntesis total de la miriaporona 4 (**1**). El esquema retrosintético que nos planteamos se recoge en el Esquema 3. La retrosintesis se basa en la desconexión de la molécula **1** en dos aldehídos (**11-13** y **16**) y una cetona (**14-15**) que se unen mediante dos reacciones aldólicas estereoselectivas.[8], una para la formación del enlace C8-C9 con

[8] (a) Reiser, O.; Mengel, A. *Chem. Rev*. **1999**, *99*, 1191.(b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1-76

una configuración relativa *anti*[9] y la otra para formar el enlace C5-C6 con configuración relativa *syn*.[10]



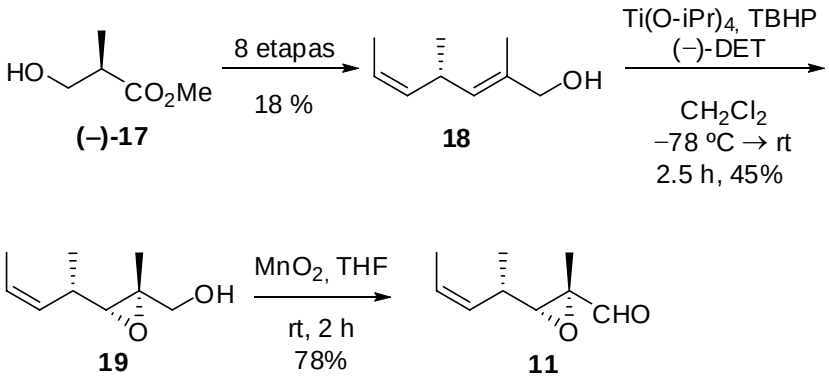
Esquema 3

Para la síntesis del aldehído **11** nos basamos en la síntesis del tedanólido **2** publicada por Kalesse.[11] A partir del hidroxiester comercial **(–)-17** se obtiene el alcohol α,β-insaturado **18** el cual, mediante una epoxidación de Sharpless y posterior oxidación del grupo hidroxilo de **19** nos permite acceder al aldehído **11** (Esquema 4).

9 a)Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747-5750. b) Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213-1214. c) Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T.-H. *J. Org. Chem.***1996**, *61*, 2038-2043.

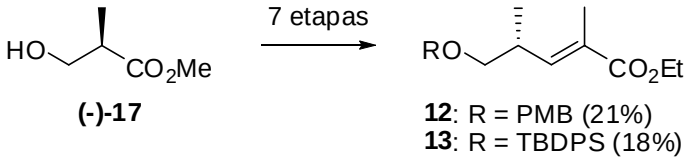
10 Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586-2587.

11 Hassfeld, J.; Kalesse, M. *Synlett* **2002**, 2007-2010.



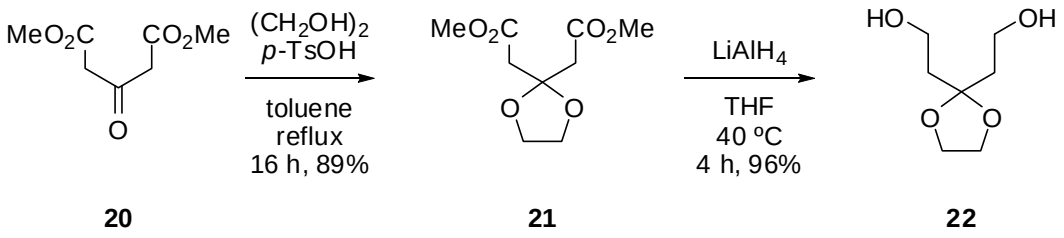
Esquema 4

De manera análoga se sintetizaron los aldehídos **12** y **13** con buen rendimiento (Esquema 5).



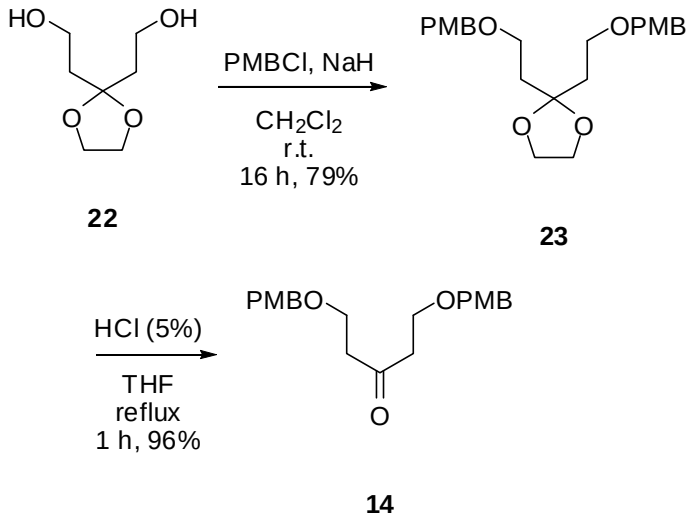
Esquema 5

Para la síntesis de las cetonas **14**-**15** obtuvimos un intermedio común, el diol **22** que obtuvimos a partir del cetodiester comercial **20** (Esquema 6).



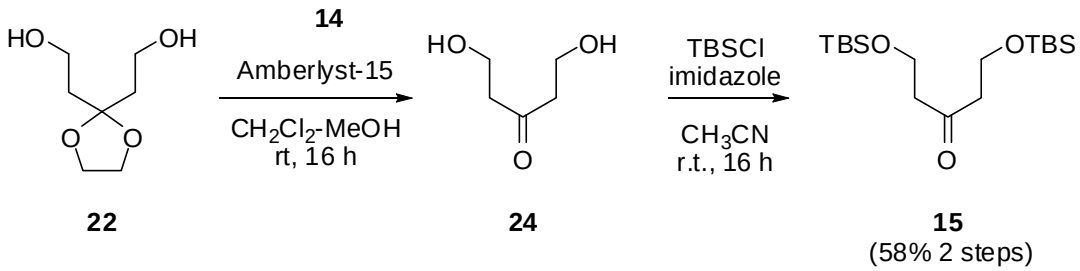
Esquema 6

Posteriormente, para la síntesis de **14** seguimos el procedimiento detallado en el Esquema 7. Protegiendo el diol **22** en forma de *p*-metoxibencilo se obtiene **23** que tras hidrólisis del acetal da la cetona **14** deseada.



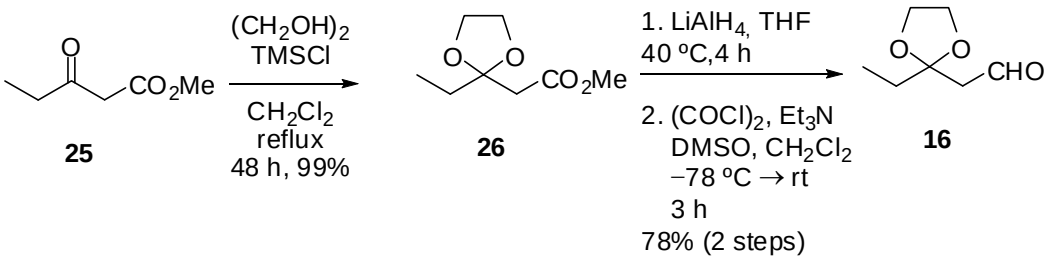
Esquema 7

Para la síntesis de **15** no pudimos seguir la misma ruta que la de la obtención de **14**, puesto que en el paso de hidrólisis del acetal los grupos *t*-butildimetilsilanos también se hidrolizaban. Por lo tanto la estrategia que seguimos consistía en la hidrólisis del acetal del compuesto **22** para obtener la dihidroxicetona **24** que por su tamaño y polaridad no se aislaba por lo que directamente la tratábamos con TBSCl para obtener la cetona **15** Esquema 8).



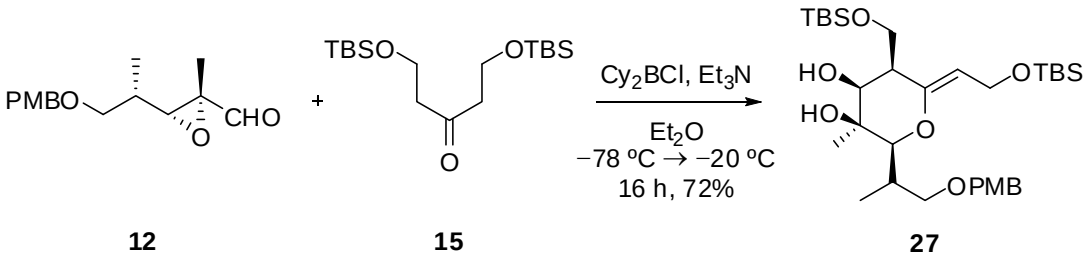
Esquema 8

El tercer fragmento de la molécula **1**, el aldehído **16** se sintetizó a partir del cetoester **25** cuya cetona se protegió en forma de acetal (**26**), el cual mediante una secuencia de reducción-oxidación se transformó en el aldehído **16** (Esquema 9).



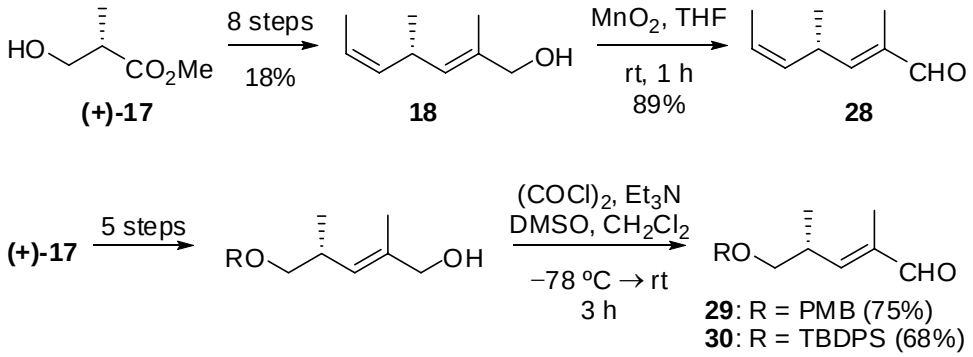
Esquema 9

La reacción aldólica entre el aldehído **12** y la cetona **15** dio lugar a un producto inesperado, el pirano **27**. Durante la reacción el epóxido se rompía dando como único producto de la reacción el ciclo (Esquema 10).



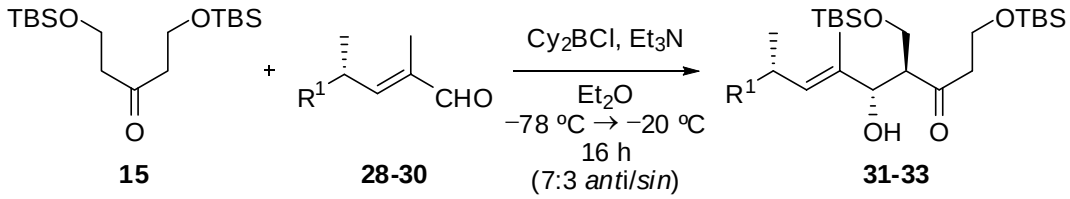
Esquema 10

Después de este resultado decidimos posponer la introducción del oxirano a los pasos finales de la síntesis de **1** por lo que sintetizamos los análogos **28-30**. Para la síntesis de estos productos seguimos un procedimiento análogo al de la obtención de **11-13**, las etapas seguidas se resumen en el siguiente (Esquema 11).



Esquema 11

La reacción aldólica entre la cetona **15** y los aldehídos **28-30** se realizó utilizando las condiciones descritas por Paterson[12] para la obtención de aldoles de configuración relativa *anti*. Se realizaron diversas reacciones aldólicas modelo para poner a punto las condiciones de reacción empleando diversos aldehídos comerciales de estructura similar a la del fragmento real de la miriaporona 4 (**1**). Finalmente obtuvimos los aldoles **31-33** (Esquema 12).



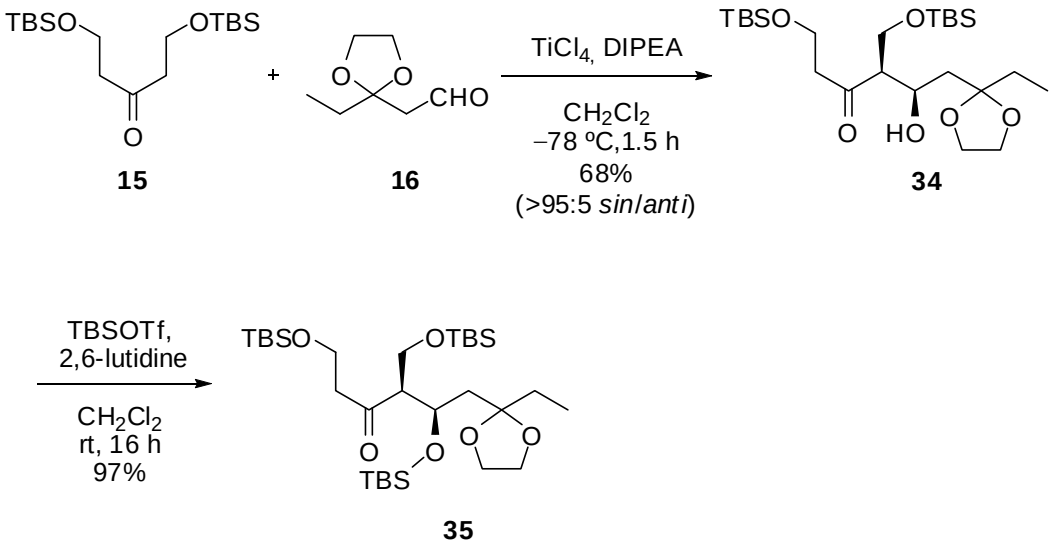
15 **28-30** **31-33**

Entrada	**Aldehído**	**R^1**	**Aldol**	**Rdto. (%)**	**dr (*anti*:*sin*)**
1	**28**	(*Z*) -CH=CHMe	**31**	72	7:3
2	**29**	-CH_2OPMB	**32**	81	7:3
3	**30**	-CH_2TBDPS	**33**	89	7:3

Esquema 12

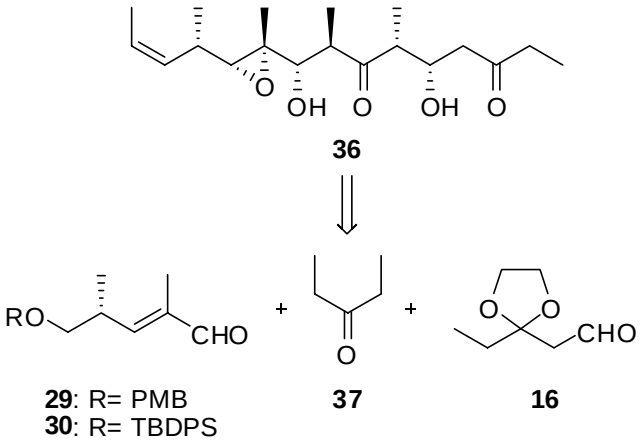
Posteriormente se intentó la reacción aldólica con configuración relativa *sin* entre **31-33** y el aldehído **16** sin éxito. Por lo que decidimos cambiar la estrategia de síntesis uniendo los tres fragmentos en que habíamos dividido la molécula en otro orden, es decir, uniendo primero la cetona **15** con el aldehído **16** y por último introduciendo el fragmento **31-33**. La reacción aldólica entre **15** y **16** se hizo empleando Bu_2BOTf y DIPEA con el fin de obtener la relación *sin* en los centros generados en la reacción, pero sólo se recuperaron los productos de partida. Probamos la enolización de **15** con Ti (IV). En estas condiciones se obtuvo el aldol **34** cuyo OH se protegió como TBS obteniendo el producto **35**(Esquema 13).

12 Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585-8588.



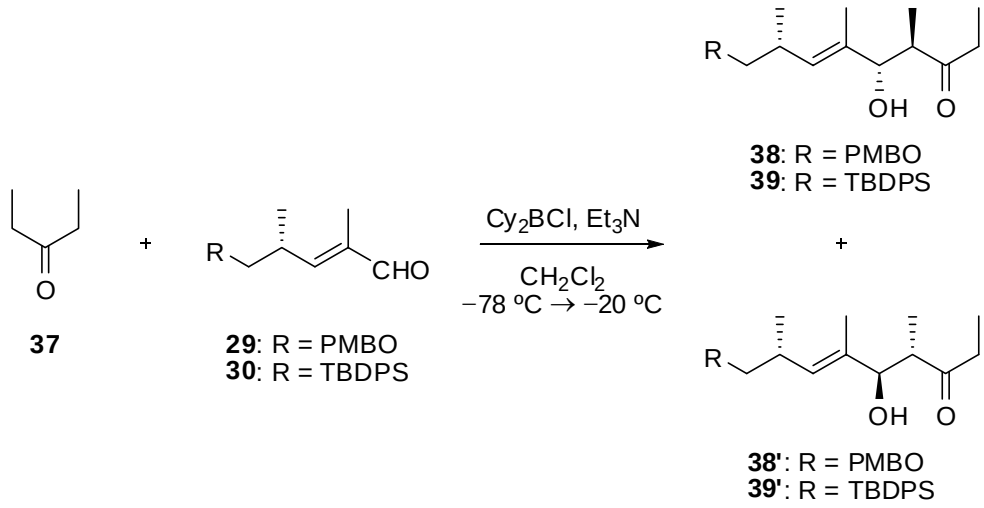
Esquema 13

Al hacer reaccionar **35** con cualquiera de los aldehídos **28-30** sólo se obtuvieron los productos de partida. Con objeto de evitar el posible impedimento estérico que ejercen los grupos TBS de la cetona **15** se planteó la síntesis del derivado **36**, el cual es la versión desoxidada de **1.** Para la síntesis de **36** se planteó una retrosíntesis análoga a la de **1** empleando 3-pentanona (**37**) en lugar de la cetona **15** y los aldehídos **29-30** (Esquema 14).



Esquema 14

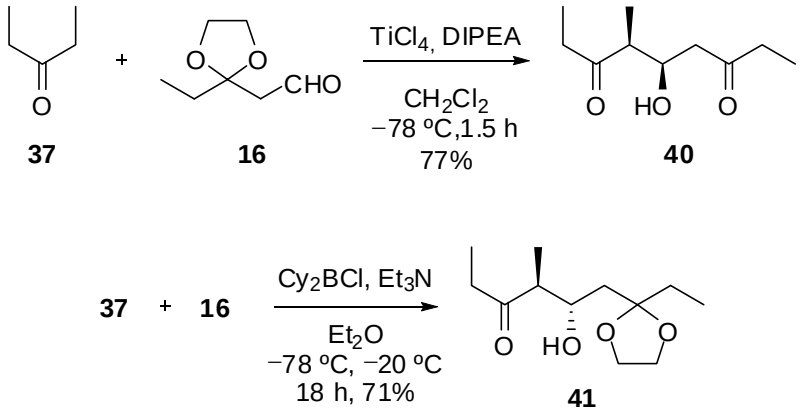
Los aldoles **38/38'-39/39'** se obtuvieron como mezcla inseparable de diasterómeros 1:1 *anti/sin* con buen rendimiento mediante reacción aldólica entre **37** y **29-30** (Esquema 15). Posteriormente se probó la reacción entre **38-39** y el aldehído **16** sin éxito.



Aldehyde	Products	Yield (%)
29	**38/38'**	91
30	**39/39'**	98

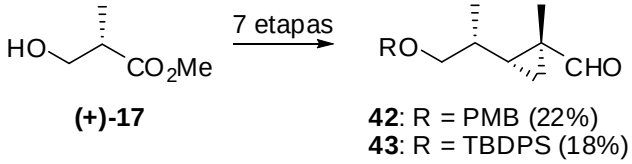
Esquema 15

A la vista de estos resultados se volvió a intentar la estrategia de unir los fragmentos en diferente orden. El aldol **40** se obtuvo mediante la reacción entre la cetona **37** y el aldehído **16**, en el medio de reacción el acetal se hidroliza por lo que la síntesis no se podía seguir por este camino. Se probaron otras condiciones para obtener el aldol de configuración relativa *sin* pero sin éxito por lo que finalmente se decidió continuar la síntesis con el aldol de configuración relativa *anti* (**41**) obtenido haciendo uso de Cy_2BCl y Et_3N (Esquema 16). Pero una vez más todos los intentos para unir el aldol **41** con el fragmento **29-30** fracasaron y sólo se recuperaron los productos de partida.



Esquema 16

Otro objetivo de esta tesis es la síntesis de derivados de **1** para medir su actividad antitumoral. Así pues se sintetizaron los derivados ciclopropanados **42-43** (Esquema 17). Para la etapa de ciclopropanación se emplearon las metodologías decritas por Simmons y Smith[13] y también la de Charette[14] obteniendo resultados similares en ambos casos. **42-43** se obtienen a partir del hidroxiester comercial **(+)-17** en 7 etapas con un rendimiento del 22% y del 18% respectivamente.

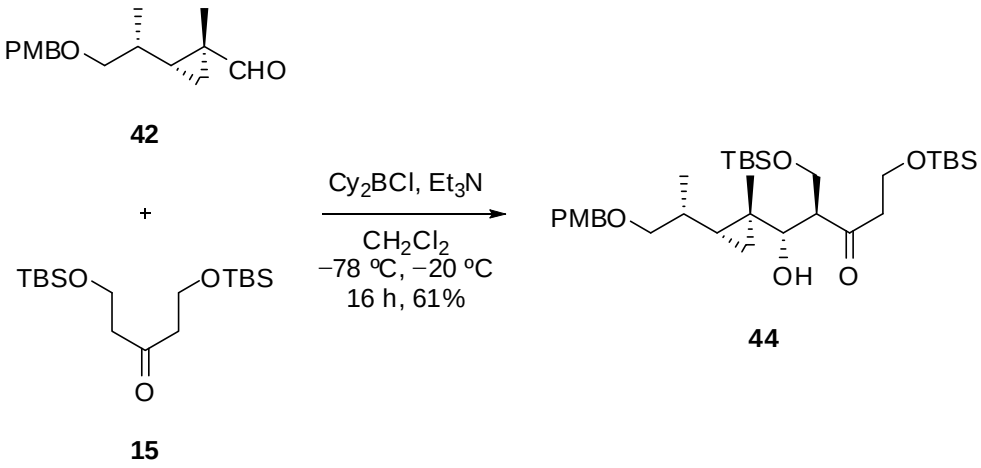


Esquema 17

De esta manera se obtuvo el aldol **44** resultante de la reacción entre **15** y **42** (Esquema 18). La reacción entre **44** y el aldehído **16** para unir los tres fragmentos nos condujo una vez más a recuperar los productos de partida inalterados.

13 (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256-4264. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.*, **1958**, *80*, 5323-5324.

14 Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977-1050.



Esquema 18

Finalmente se probó la actividad biológica de los nuevos intermedios sintetizados en este trabajo (**11**, **40-41**, **45-49**) (Figura 3), para ello se eliminaron todos los grupos protectores. Ningún intermedio resultó activo frente a las dianas probadas.

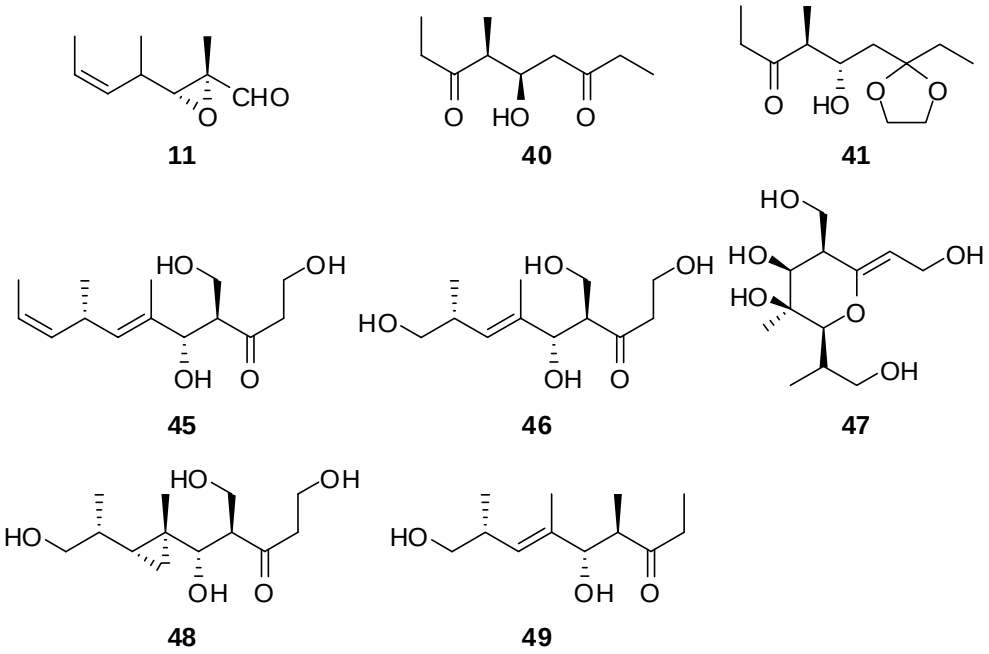


Figura 3

In this document the abbreviations and acronyms most commonly used in organic chemistry have been used, according to the recommendations of "*Guidelines for authors" J. Org. Chem.* **2007**, *72*, 23A-24A.

Additionally, the following abbreviations and acronyms have been used:

Cy	cyclohexyl
TBAF	tetrabutylamonium fluoride
IBX	*o*-iodoxybenzoic acid

INTRODUCTION

1. The sea as a source of medicinal natural products

Our planet offers a wide diversity of life, with an extraordinary number of animal and vegetal species that have evolved to adapt to their different ecosystems. As a consequence of this adaptation a huge variety of chemical structures are produced by these numerous species. In no other place the biological spectrum is as extensive as in the sea, which covers 70% of the earth surface. The immense majority of the animal families, or phyla, are related to the sea: 33 of the 34 animal phyla are of marine origin. During the past 30 years a very large number of novel marine natural products with useful and sometimes extraordinary pharmacological properties have been reported.[1]

In order to evaluate the biomedical potential of any organism, both the chemical ecology of the organism and its evolutionary history must be considered. It is probable that chemical defense mechanisms evolved with the most primitive microorganisms but have been replaced in many more advanced organisms by physical defenses and/or the ability to run or swim away and hide. The specific evolutionary pressures that led to chemically rich organisms need not be defined but with a longer period of evolution,

1 (a) Blunt, J. W.; Copp. B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1-49. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1-48. (c) Jiménez, J. C.; Marfil, M.; Francesch, A.; Cuevas, C.; Álvarez, M.; Albericio, F. *Investigación y Ciencia* **2007**, 365-374.

the surviving organism has had more time to perfect its chemical arsenal. Sessile, soft-bodied marine invertebrates, without physical defenses, have had ample opportunity to improve their chemical defenses during millions of years and are therefore prime candidates to posses bioactive metabolites.

Among the many phyla found in the oceans, the best sources of pharmacologically active compounds are bacteria, fungi, certain groups of algae, sponges, soft corals, nudibranchs, bryozoans, and tunicates. Some marine organisms such as dinoflagellates, echinoderms and some fish are known for their ability to produce potent toxins, but these are usually too toxic for medicinal use.

Chemical defense mechanisms cannot be directly related with potential biomedical activity, but it is remarkable how well the two correlate in reality.[1b] Nature has continuously provided a broad and structurally diverse arsenal of pharmacologically active compounds that are still used as highly effective drugs to combat a multitude of deadly diseases or as lead structures for the development of novel synthetic derivatives. Traditionally, higher plants and, since the discovery of the penicillins, terrestrial microorganisms had proven to be the richest sources of natural drugs that are indispensable especially for the treatment of diseases such as cancer. Well known examples of plant-derived anti-cancer drugs include paclitaxel (taxol), from *Taxus brevifolia*,[2] etoposide (vepesid), derived by partial synthesis from the lignan podophyllotoxin isolated from *Podophyllum peltatum*,[3] and irinotecan (campthosar), which was obtained by optimizing the structure of the alkaloid camptothecin from *Camptotheca acuminata*.[4] Examples from bacterial sources include doxorubicin (adriamycin) and bleomycin from various *Streptomyces* strains.[5]

2 Huang, C. H. O.; Kingston, D. G. I.; Magri, N. F.; Samaranayake, G.; Boettner, F. E. *J. Nat. Prod.* **1986**, *49*, 665-669.

3 Kutney, J. P.; Chen, Y. P.; Gao, S.; Hewitt, G. M.; Kuri-Brena, F.; Milanova, R. K.; Stoynov, N. M. *Heterocycles* **1993**, *36*, 13-20.

4 (a) Curran, D. P.; Ko, S.-B.; Josien, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2683-2684. (b) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc*. **1966**, *88*, 3888-3890.

5 Rishel, M. J.; Hecht, S. M. *Org. Lett.* **2001**, *3*, 2867-2869.

Serious attempts to explore the potential of marine organisms as sources of bioactive metabolites started in the late 1960s. The discovery of sizeable quantities of prostaglandins in the gorgonian *Plexaura homomalla*[6] in 1969 is considered as the "take-off point" of the drug search from the sea.

In the last three decades, approximately 300 patents on bioactive marine natural products were issued. Since the beginnings, the number of compounds isolated from various marine organisms exceeds 10000, with hundreds of new compounds still being discovered every year.[1] Through the combined efforts of marine natural product chemists and pharmacologists, a number of promising compounds that have been identified are at advanced stages of clinical trials or have been selected as promising candidates for extended preclinical evaluation. The majority of marine natural products currently in clinical trials or under pre-clinical evaluation are produced by invertebrates such as sponges, tunicates, mollusks or bryozoans but not by algae. This is in sharp contrast to the terrestrial environment where plants by far exceed animals with regard to the production of bioactive natural products (also called secondary metabolites). The wealth of bioactive metabolites isolated from sessile or slowmoving marine invertebrates that usually lack morphological defense structures such as spines or a protective shell is no coincidence and reflects the ecological importance of these constituents for the respective invertebrates. It has been repeatedly shown that chemical defense through accumulation of toxic or distasteful natural products is an effective strategy to fight off potential predators (e.g. fishes) or to force back neighbors competing for space. The majority of drug candidates from the sea have so far been isolated from invertebrates that thrive in tropical or subtropical seas where the grazing pressure by predators such as fishes is higher than in any other ecosystem of the world.[7] Under these severe selective pressures only those organisms that can rely on effective means of chemical defense will survive. Thus, organisms that thrive in spite of pronounced biotic pressures can be expected to contain metabolites that are of interest for drug prospectors searching the oceans.

6 Light, R. J.; Samuelsson, B. *Eur. J. Biochem.* **1972**, *28*, 232-240.

7 On tropical coral reefs fish have been estimated to bite the bottom in excess of 150,000 times per m^2 and day. Proksch, P.; Edrada, R. A.; Ebel, R. *Appl. Microbiol. Biotechnol.* **2002**, *59*, 125–134.

Marine natural products such as the ion channel-blockers tetrodotoxin and saxitoxin and the phosphatase inhibitor okadaic acid have long been used extensively as research tools. More recent research into marine sources has led to the discovery of novel anticancer drug candidates, such as eteinascidin-743 (a transcription inhibitor from *Ecteinascidia turbinate),*[8] didemnin B (a protein translation inhibitor from *Tridemnum solidum*),[9] discodermolide (a microtubule stabilizer/senescence accelerator from *Discodermia sp*.),[10] tedanolide (a cytotoxic agent from *tedania ignis*),[11] 13-deoxytedanolide (agonist of SAPK/JNK and p38 MAP kinases from *Mycale adhaerens*),[12] and myriaporone 3 and 4 (cytotoxic agent from *Myriapora truncata)*.[18]

The next Table 1 shows the status of some of the most outstanding marine-derived natural products in clinical trials against several cancer types.[13]

Name	**Source**	**Phase**
Didemnin B	*Tridemnum solidum*	II
Dolastatin 10	*Dolabella auricularia*	I/II
Girolline	*Pseudaxinyssa cantharella*	I
Bengamide derivative	*Jaspis sp.*	I
Cryptophycins	*Nostoc sp. & Dysidea arenaria*	I

8 (a) Friedman, D.; Hu, Z.; Kolb, E. A;. Gorfajn, B.; Scotto, K. W. *Cancer Res.*, **2002**, *62*, 3377–3381. (b) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2,* 2545-2548.

9 Crews, C. M.; Collins, J. L.; Lane, W. S.; Snapper M. L.; Schreiber, S. L. *J. Biol. Chem.*, **1994**, *269*, 15411–15414.

10 (a) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.*, **1996**, *3*, 287–293. (b) Klein, L. E.; Freeze, B. S.; Smith, A. B., III; Horwitz, S. B. *Cell Cycle*, **2005**, *4*, 501–507.

11 Schmitz, F.J.; Gunasekera, S.P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251-7252.

12 Fusetani, N.; Sugawara, T.; Matsunaga, S.; Hirota, H. *J. Org. Chem.* **1991**, *56*, 4971-4974.

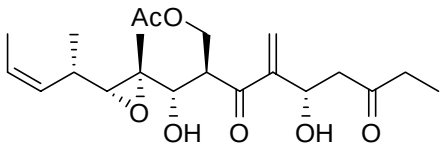
13 Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2004**, *67*, 1216-1238.

Bryostatin	*Bugula neritina*	II
TZT-1027	Synthetic dolastatin	II
Cematodin	Derivative of dolastatin 15	I/II
ILX 651	Derivative of dolastatin 15	I/II
Ecteinascidin 743	*Ecteinascidia turbinata*	II/III
Aplidine	*Aplidium albicans*	II
E7389	*Lissodendoryx sp.*	I
Discodermolide	*Discodermia dissolute*	I
Discodermolide	*Discodermia dissolute*	I
Kahalalide F	*Eylsia rufescens/Bryopsis sp.*	II
ES-285 (spisulosine)	*Spisula polynyma*	I
HTI-286	*Cymbastella sp.*	II
KRN-7000	*Agelas mauritianus*	I
Squalamine	*Squalus acanthias*	II
Tedanolide	*Tedania Ignis*	I
Myriaporone 4	***Myriapora truncata***	**I**
13-Deoxitedanolide	*Mycale adhaerens*	I
Neovastat	*Shark cartilage*	II/III

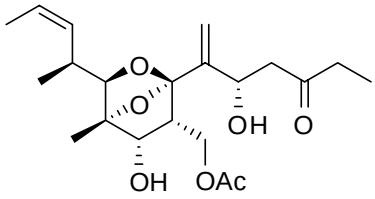
Table 1

2. Myriaporone in Nature. Isolation and characterization

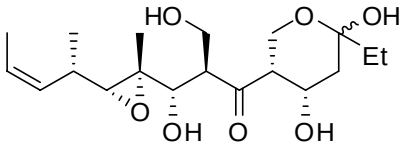
There are four naturally occuring myriaporones **1-4** (Figure 1).



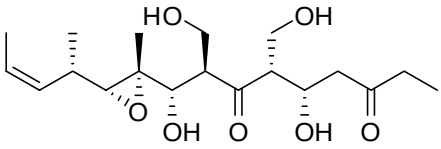
1: Myriaporone 1



2: Myriaporone 2



3: Myriaporone 3



4: Myriaporone 4

Figure 1

These compounds were isolated by Rinehart in 1995[14] from the bryozoan *Myriapora Truncata,* which means "false coral" because of its appearance (Figure 2).

14 (a) Rinehart, K. L.; Cheng, J.-F.; Lee, J.-S. US patent 5,514,708, **1996**. (b) Rinehart, K. L.; Tachibana, K. *J. Nat. Prod.* **1995**, *58*, 344-358.

Figure 2

The bryozoans are a group of primitive colonial animals widely distributed throughout the world's marine and fresh-water enviroments.[15] *Myriapora truncata* is collected in the Western Mediterranean.

The characterization of myriaporone 4 (**4**) was firstly described by Reinehart[14], and the absolute configuration determined by PharmaMar[16] and Taylor[17] by total synthesis. This molecule of only thirteen carbons is very densely funcionalized. The main structural features of myriaporone 4 (**4**) are an oxirane ring, a *Z*-olefin, four hydroxyl groups and seven stereocenters (Figure 3).

15 (a) Christophersen, C. *Acta Chem. Scand Ser.B,* **1985**, *39*, 517-529; (b) Faulkner, D. J. *Nat. Prod. Rep.* **1993**, *10*, 497-539.

16 Pérez, M.; del Pozo, C.; Reyes, F.; Rodríguez, A.; Francesch, A.; Echavarren, A. M.; Cuevas, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 1724-1727.

17 (a) Fleming, K. N.; Taylor, R. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1728-1730. (b) Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Org. Lett.* **2002**, *4*, 2953-2955. (c) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361-9364.

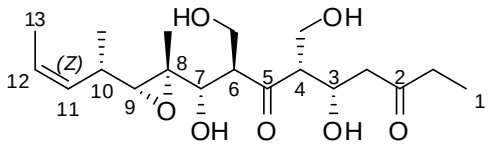
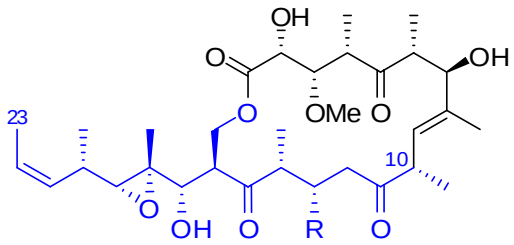


Figure 3

3. Structural relations between myriaporone 4 and tedanolide

Myriaporone 4 (**4**) is structurally related to the C10-C23 region of the macrolides tedanolide **5** and deoxytedanolide **6** (Figure 4). The structure of myriaporone 4 (**4**) is shown in blue in Figure 4 overlapped to the structure of **5** and **6**.



5 R = OH
6 R = H

Figure 4

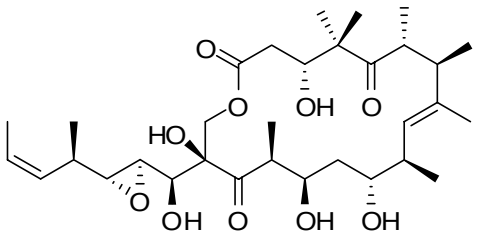
Tedanolide (**5**) is a potent cytotoxic macrolide isolated from the Caribbean sponge *Tedania ignis*.[18] The *in vitro* biological data of tedanolide is remarkable, with ED_{50}= 0.25 ng/mL in KB cells and 1.6 pg/mL in PS cells, and causes accumulation of cells at the S face in the cell cycle at concentrations as low as 0.01 µg/Kg. *In vivo*,

18 (a) Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; Van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251-7252. (b) O'Hagan, D. *Nat. Pod. Reports* **1993**, 593-625.

tedanolide has been shown to increase the lifespan of mice implanted with lymphocytic leukemia by 23% at 1.5 µg/Kg body weight.

Fusetani and co-workers reported the isolation of 13-deoxytedanolide (**6**) from the marine sponge *Mycale adhaerens.*[19] This related molecule also showed extraordinary biological activity, exhibiting an IC_{50} of 94 pg/mL against P388 murine leukemia cell lines, with a T/C value of 189% at a dose of 0.125 mg/Kg.

More recently, Ireland *et al.* reported the isolation of tedanolide C (**7**) (Figure 5) from the marine sponge *Ircina sp*,[20] which exhibits less biological activity than the other two tedanolides (**5** and **6**). In this case the C13-C23 region is not too similar to myriaporone 4 (**4**) .



7

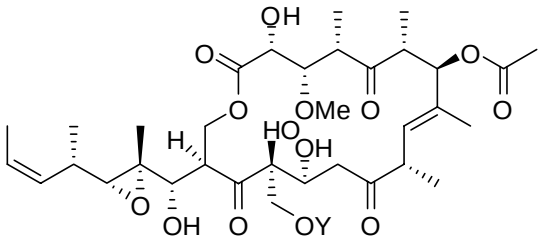
Figure 5

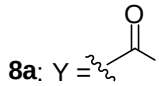
As natural analogues of tedanolide, must be mentioned the candidaspongiolides **8a** and **8b** (Figure 6) described recently by McKee *et al*[21]. Which are acyl esters isolated from sponges of the genus *Candidaspongia* and present antitumor activity.

19 Fusetani, N.; Sugawasara, T.; Matsunaga S. J. *J. Org. Chem.* **1991**, *56*, 4971-4973.

20 Chevallier, C.; Bugni, T. S.; Feng, X.; Haper, M. K.; Orendt, A. M.; Ireland, C. M. *J. Org. Chem.* **2006**, *71*, 2510-2513.

21 Meragelman, T. L.; Willis, R. H.; Woldemichael, G. M.; Heaton, A.; Murphy, P. T.; Snader, K. M.; Newman, D. J.; van Soest, R.; Boyd, M. R.; Cardellina II, J. H.; McKee, T. C. *J. Nat. Pod.* **2007**, *70*, 1133-1138.





8a: Y = R R = $C_{13}H_{27}$; $C_{14}H_{29}$; $C_{15}H_{31}$; $C_{16}H_{33}$; $C_{17}H_{35}$; $C_{17}H_{33}$

8b: Y = H

Figure 6

As a result of the limited availability of both myriaporones (**1-4**) and tedanolides (**5-7**), their biology remains unknown.

4. Myriaporone 4 activity and structure-activity relationship

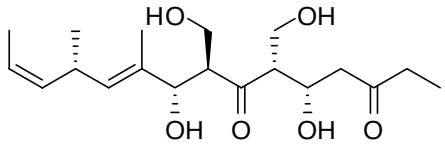
Recently, Taylor and Crews reported a structure-activity relationship of myriaporone to define a pharmacophore eukaryotic protein synthesis.[22]

The biological activity of myriaporone 4 (**4**) was examined against two different mammalian cells: P388 mouse leukemia cells and bovine aortic endothelial cells. The former is a transformed cell line which grows in suspension and the latter are adherent, primary cells. Despite significant differences in the growth patterns of these cells, myriaporone 4 (**4**) effectively inhibited the proliferation of both with IC_{50} values in the low nanomolar range (IC_{50} = 15.9 ± 1.0 nM for endothelial cells; IC_{50} = 15.4 ± 1.7 nM for P388 cells), which is approximately 18-fold more potent than was reported in the initial discovery of myriaporone.[14]

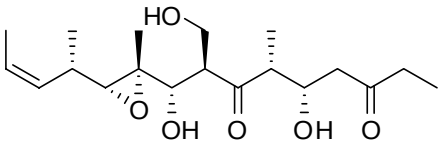
22 Hines, J.; Roy, M.; Cheng, H.; Agapakis, C. M.; Taylor, R.; Crews, C. M. *Mol. Biosyst.* **2006**, *2*, 371-379.

Compared in terms of potency to the known members of the tedanolide family, myriaporone 4 (**4**) falls in the middle of them: it is more potent than the recently discovered tedanolide C (**7**), but less potent than 13-deoxytedanolide (**6**)[19] or tedanolide (**5**) itself.[18] Further, the biological activity of myriaporone 4 (**4**) was not restricted to mammalian cells in assays performed on *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe.* Myriaporone 4 (**4**) inhibited the growth of both with *S. pombe* showing slightly greater sensitivity. Sensitivity of yeast to this inhibitor is not as pronounced as in mammalian cells: use of dot titration assay to determine a well-defined concentration of myriaporone 4 (**4**) that would inhibit *S. cerevisiae* proliferation showed that concentration up to and including 2 μM failed to have any effect. Moreover, deletion of the pleiotropic drug resistance membrane transport protein (*Δpdr5*) in *S. cerevisiae* failed to alter the sensitivity of *S. cerevisiae* to **4**, although the mutation did have a general growth-retarding effect. This indicates that the yeast is decreased sensitivity to myriaporone 4 (**4**) relative to that of mammalian cells is not due to more effective drug efflux. The antiproliferative activity appears to be restricted to eukaryotic organisms, in that simultaneous halo assay performed on *E. coli* did not produce any **4** growth inhibition zones (although *E. coli* was sensitive to the prokaryotic ribosome inhibitor, erythromycin).

In order to identify those functional groups of myriaporone 4 (**4**) which might be most responsible for its potent biological activity, analogues **9a-b** were synthesized by Taylor and co-workers (Figure 7).



9a



9b

Figure 7

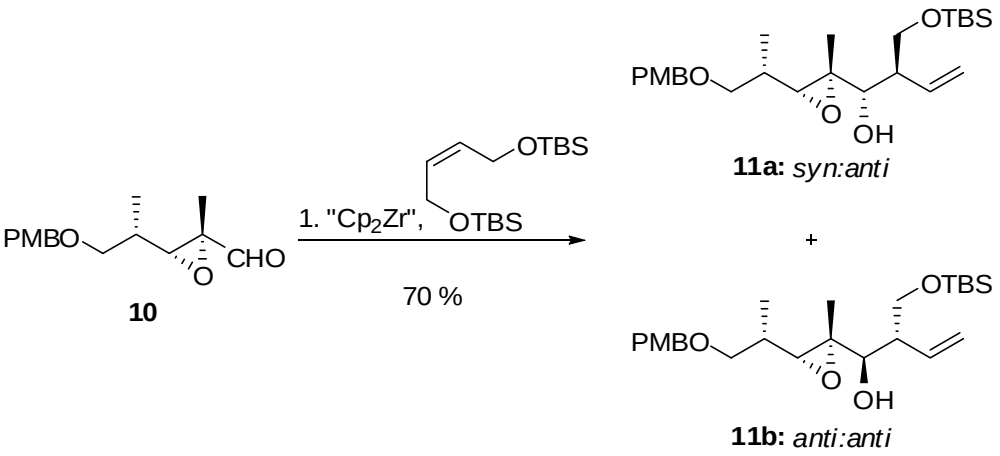
Given the evidence indicating a reversible interaction with its target, removal of the C8–C9 epoxide (**9a**) surprisingly had a profound effect on the activity of myriaporone 4, resulting in a 500- to 1000-fold decrease in activity. This unexpectedly showed that the epoxide is indeed important for activity. Replacement of the C4 hydroxymethyl group with a methyl group (**9b**) had a similar effect on the activity.

5. Synthetic approaches to the myriaporone

There are many approximations to the synthesis of tedanolide-type macrolides in the literature that makes the synthesis of myriaporones easier. In this section and in following are summarized the different scientific groups efforts to construct the skeleton of both classes of marine natural products. Only the group of PharmaMar[16] and Taylor[17] have completed the total synthesis of myriaporone 4 (**4**).

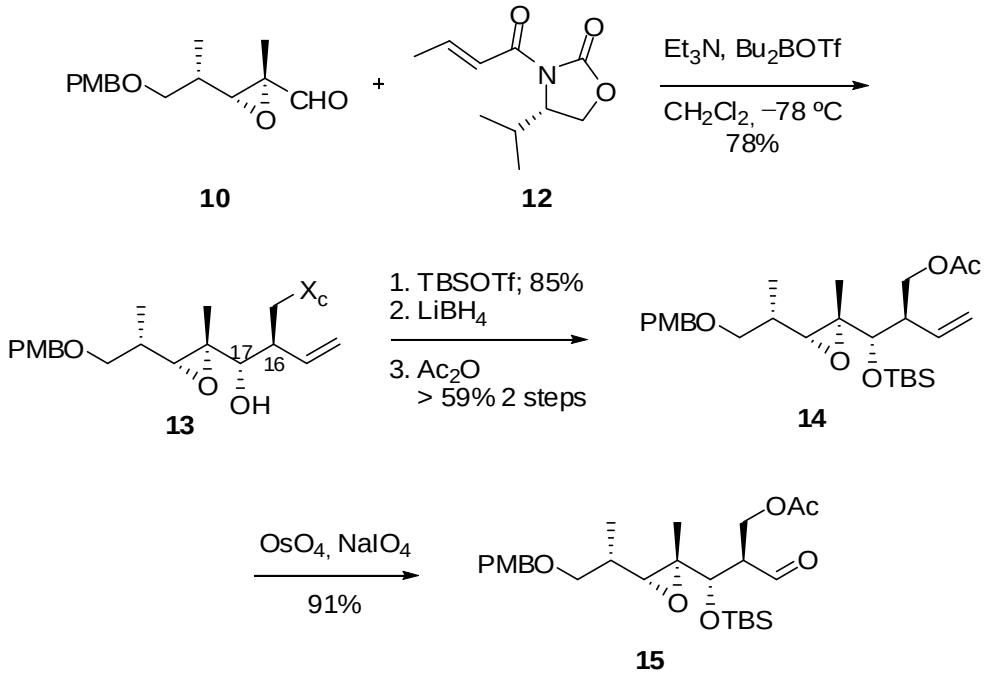
The first synthetic approach was published by Taylor in 1998.[23] In this work, Taylor described the synthesis of a common intermediate **11a** to myriaporones (**1** and **4**) and tedanolides (**7** and **8**) exploiting a zirconium allylation to generate the C16, C17 *anti* stereochemical relationship from aldehyde **10** (Scheme 1). However, with this reaction it was impossible to find the conditions to provide both high aldehyde facial stereoselectivity and the desired *anti* relative stereochemistry, and mixtures of **11a** and **11b** were obtained.

23 Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361-9364.



Scheme 1

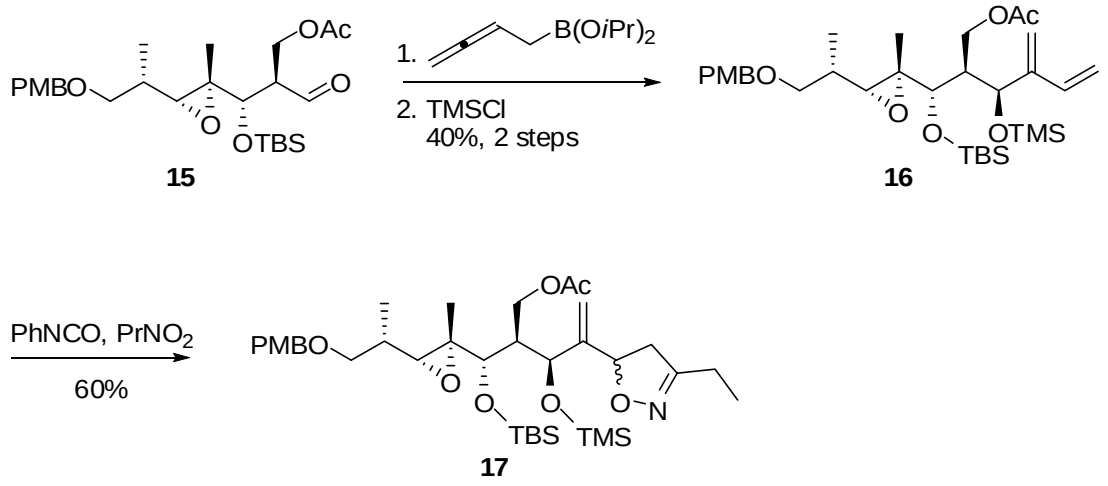
In a later work based on the sythesis of myriaporone 1 (**1**) , Taylor[24] solved this problem using an Evans oxazolidinone **12** as external chiral auxiliary, which provided the desired aldol adduct **15** (Scheme 2).



Scheme 2

24 Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Org. Lett.* **2002**, *4*, 2953-2955.

In this same work, Taylor and co-workers[24] completed the skeleton of myriaporone 1 (**1**) by a stereoselective homoallenylboration[25] and a regio- and chemoselective nitrile oxide cycloaddition[26] (Scheme 3).



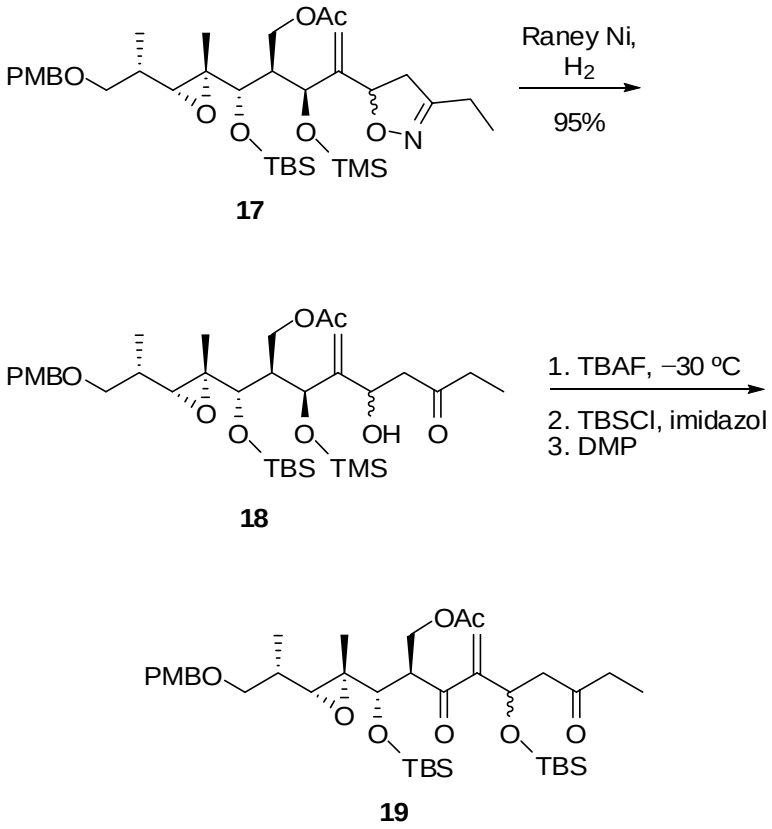
Scheme 3

Exposure of isoxazoline **17** to a Raney Ni hydrogenation in the presence of boric acid provided hydroxyketone **18** (Scheme 4). The TMS ether was selectively removed by treatment with TBAF at low temperature followed by selective protection of C13 hydroxyl and Dess-Martin oxidation[27] to give **19** Attempted deprotection of the silyl ethers of advanced intermediate **19** led to decompotition, therefore, myriaporone 1 (**1**) could not be achieved by this route.

25 Soundararajan, R.; LI, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100-104.

26 For recent work exploiting nitrile oxide cycloadditions as an alternative to aldol chemistry see: (a) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410-6424. (b) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J. *Tetrahedron Lett.* **2000**, *41*, 4151-4155.

27 Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.

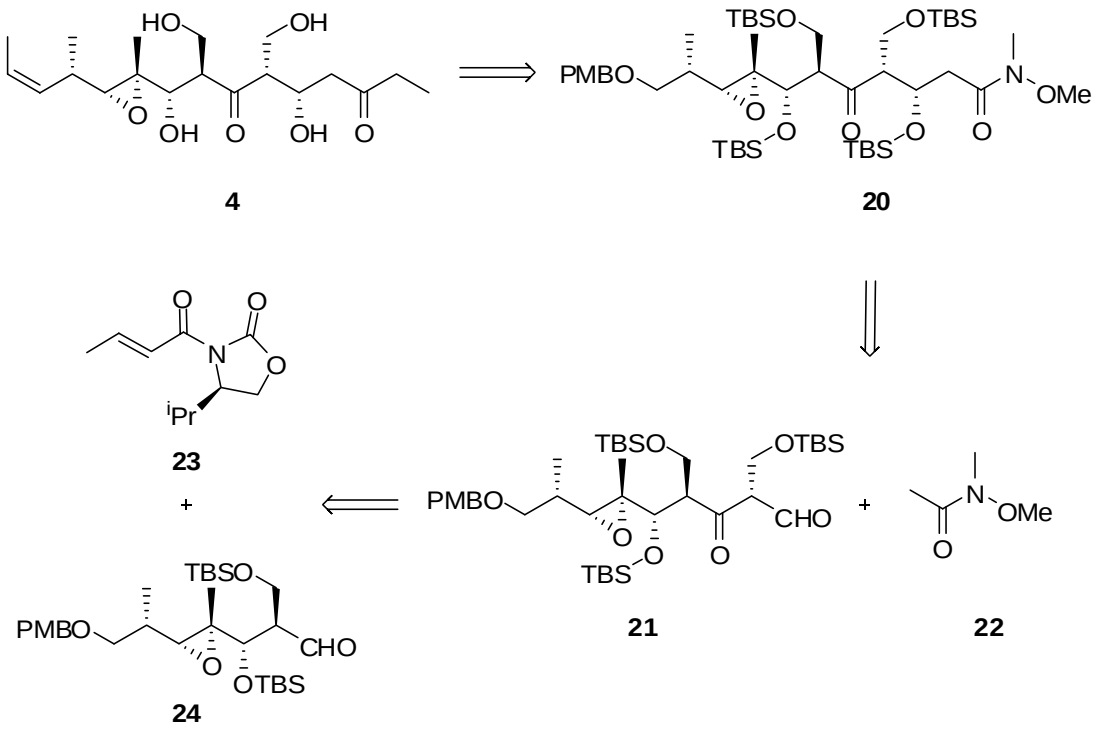


Scheme 4

5.1. The total synthesis of myriaporone by PharmaMar

The retrosynthetic approach followed by PharmaMar is outlined in Scheme 5.[28]

28 Pérez, M.; del Pozo, C.; Reyes, F.; Rodríguez, A.; Francesch, A.; Echavarren, A. M.; Cuevas, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 1724-1727.



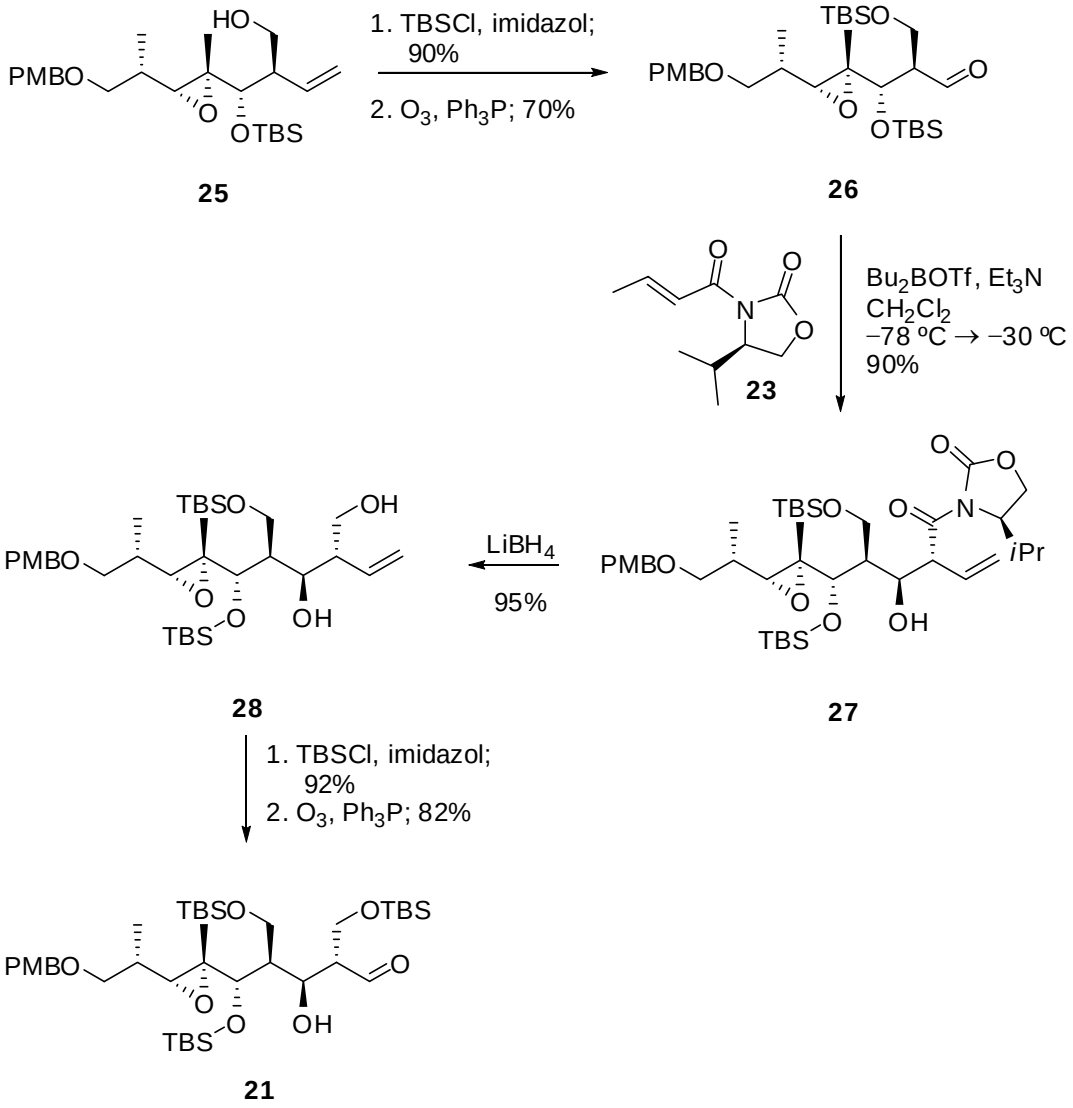
Scheme 5

The introduccion of the ethyl side chain and the *Z* alkene from Weinreb amide **20**, itself available by aldol reaction between **21** and **22** was planned. For the key of stereoselective C-C bond formation, this group relied on an Evans aldol reaction[29] between chiral oxazolidinone **23** and aldehyde **24**.[30] To avoid epimerization and retro-aldolization, oxidation of the keto group at C7 was postponed until the final steps of the synthesis.

Aldehyde **24** was prepared from **25** (Scheme 6), readily available in nine steps from methyl *(S)*-(+)-3-hydroxy-2-methylpropionate by the procedure described by Roush and Lane.[31] Protection of the primary alcohol of **25** as a TBS ether and oxidative cleavage of the olefin furnished aldehyde **26.** Reaction of the boron enolate of chiral crotonate imide **23** with **26** furnished aldol **27** with excellent diastereoselectivity

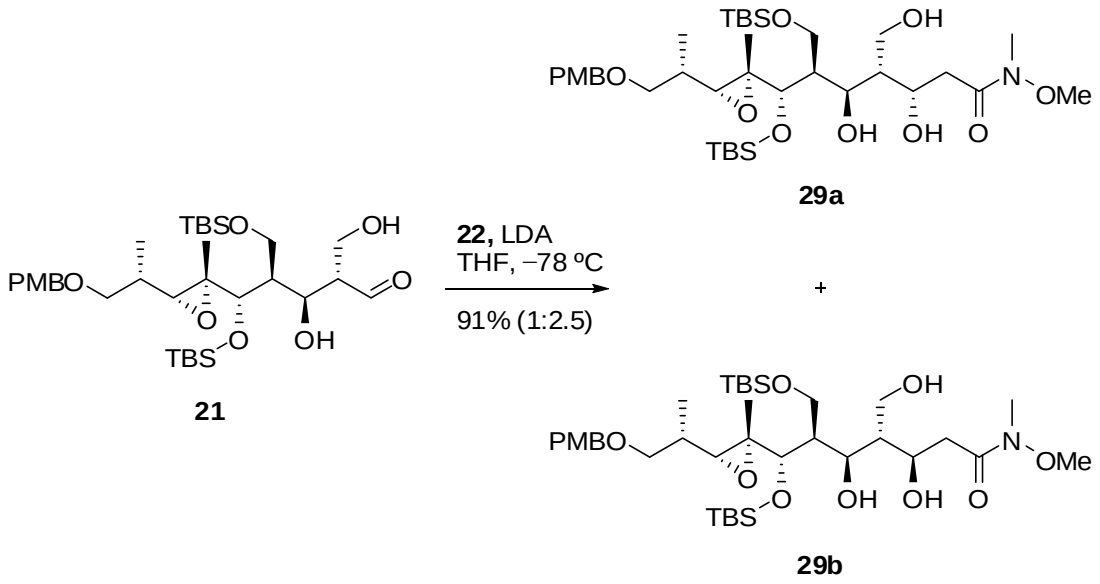
29 Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957-4960.
30 Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261-4263.
31 Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95-98.

(>99:1). Reduction of the acyl oxazolidinone and oxidative protection as TBS ether. Cleavage of the terminal double bond provided **21** with a 41% overall yield from **25.**



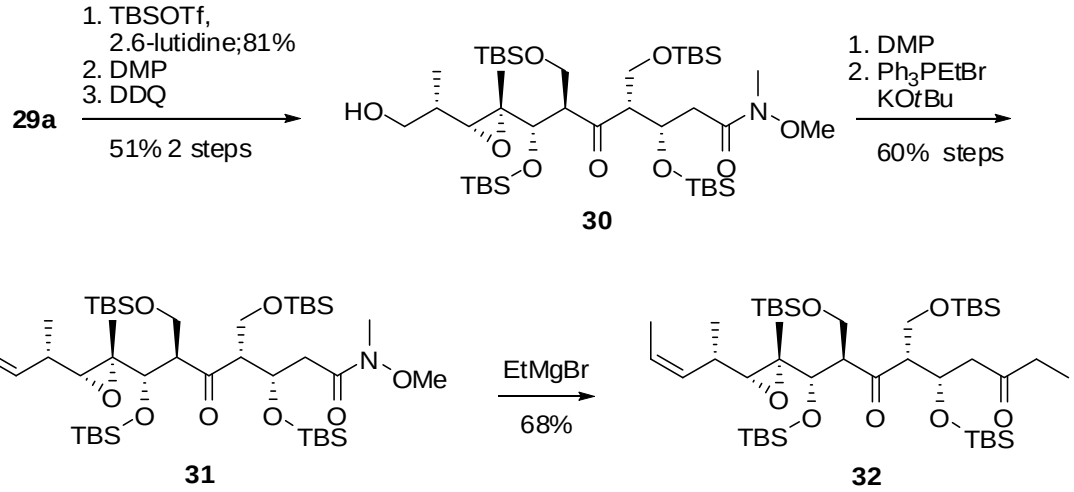
Scheme 6

Aldol reaction between aldehyde **21** and Weinreb acetamide **22** proceeded readily in the presence of LDA to give **29a** y **29b** in good yield but with low stereoselectivity (1:2.5) (Scheme 7). The use of sodium or potassium enolates of **22** furnished almost exclusively anti **29b.**



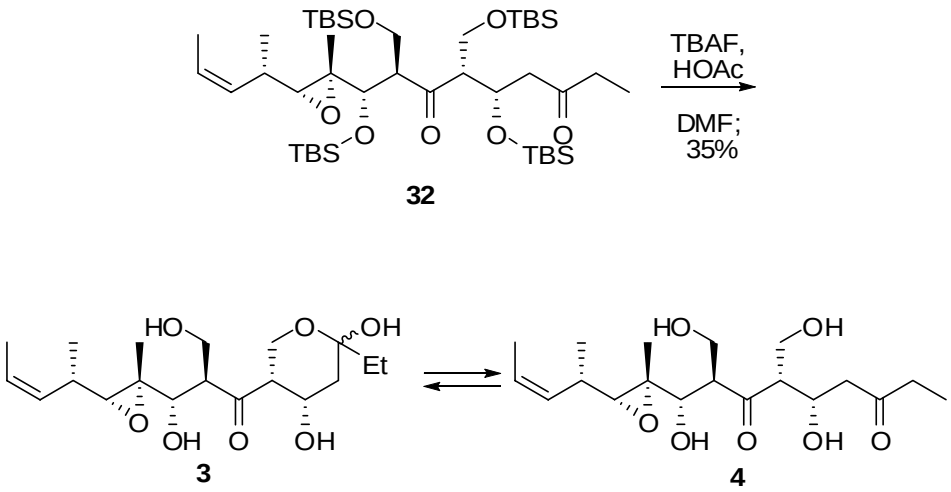
Scheme 7

Selective protection of the less hindered secondary alcohol of **29a** as TBS ether, followed by oxidation of C7 hydroxyl group and oxidative removal of the PMB group with DDQ, gave **30.** The *Z* olefin was then constructed by a Wittig reaction giving **31**. Ethyl ketone **32** was then obtained by addition of ethylmagnesium bromide to the Weinreb amide **31** (Scheme 8).



Scheme 8

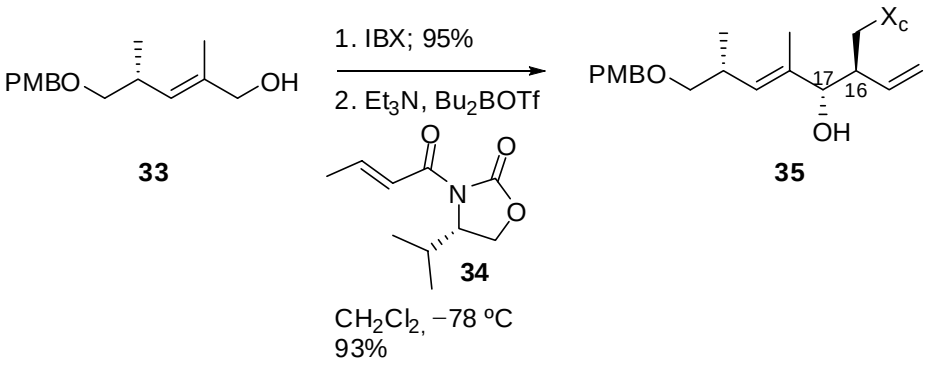
Global deprotection of the silyl ethers with TBAF/HOAc in DMF gave myriaporone 3 (**3**) and myriaporone 4 (**4**). The myriaporones **3**-**4** undergo partial dehydration on silica gel. Accordingly, acetylation of the crude dehydration products obtained after column chromatography of **3**-**4** gave myriaporone 1 (**1**) in a 35% yield over two steps (Scheme 9).



Scheme 9

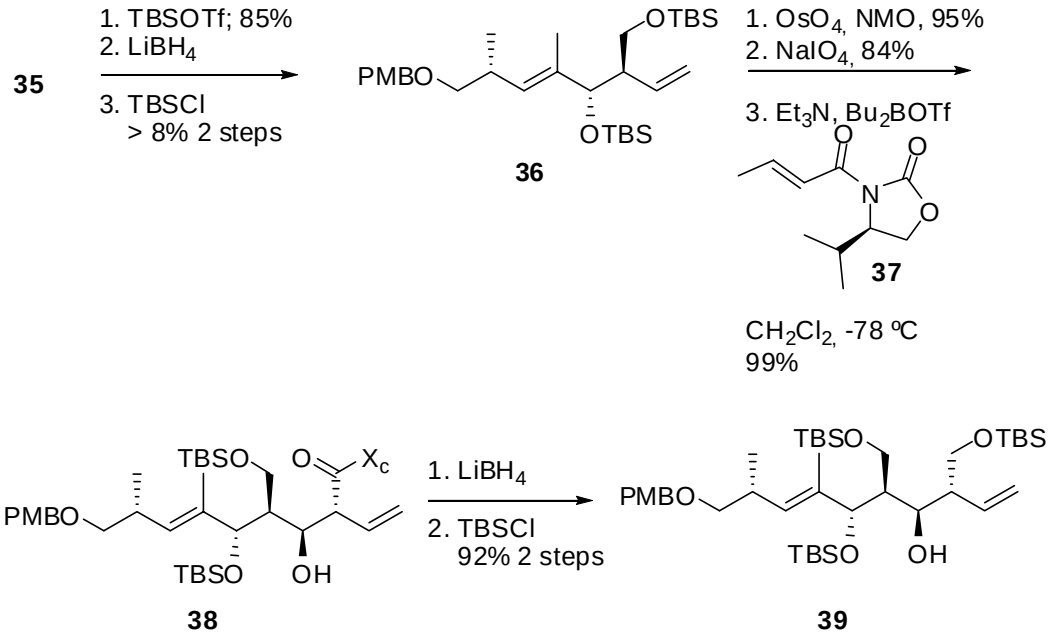
5.2. The total synthesis of myriaporone by Taylor

Following the same strategy for the completion of myriaporone **1** previously reported by the group of Taylor[23,24](see Schemes 1-4 of this section) Scheme 2. Construction of myriaporone 4 (**4**) began with known alcohol **33** (Scheme 10).[17] Oxidation with IBX followed by an Evans aldol reaction gave **35**.



Scheme 10

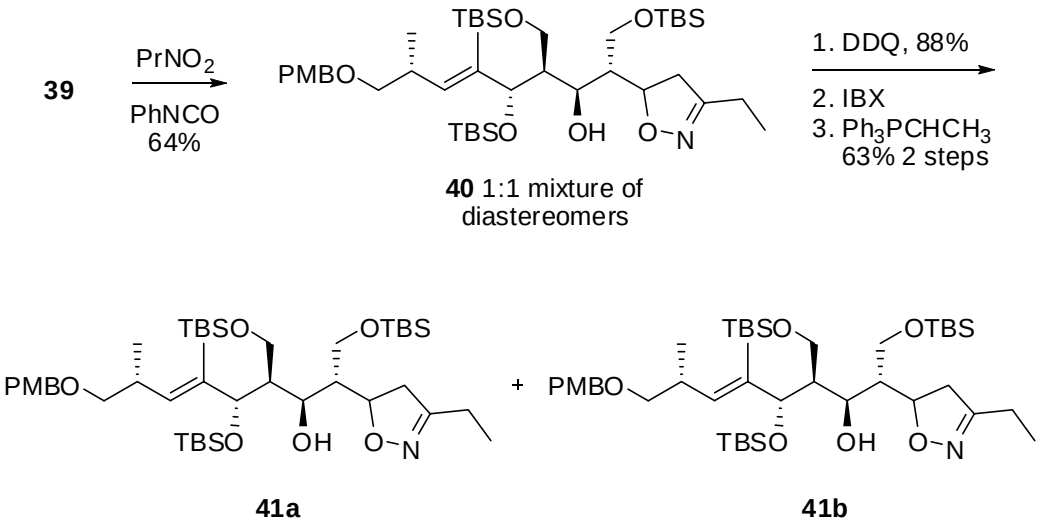
Aldol **35** was converted into bis-TBSether **36** by protection, reductive cleavage of the chiral auxiliary, and a second protection step. Oxidative cleavage of the terminal olefin was followed by a second Evans aldol reaction with oxazolidinone **37** reaction to provide **38** in excellent yield. The chiral auxiliary was removed reductively and the primary alcohol was protected with TBSCl to provided **38** (Scheme 11).



Scheme 11

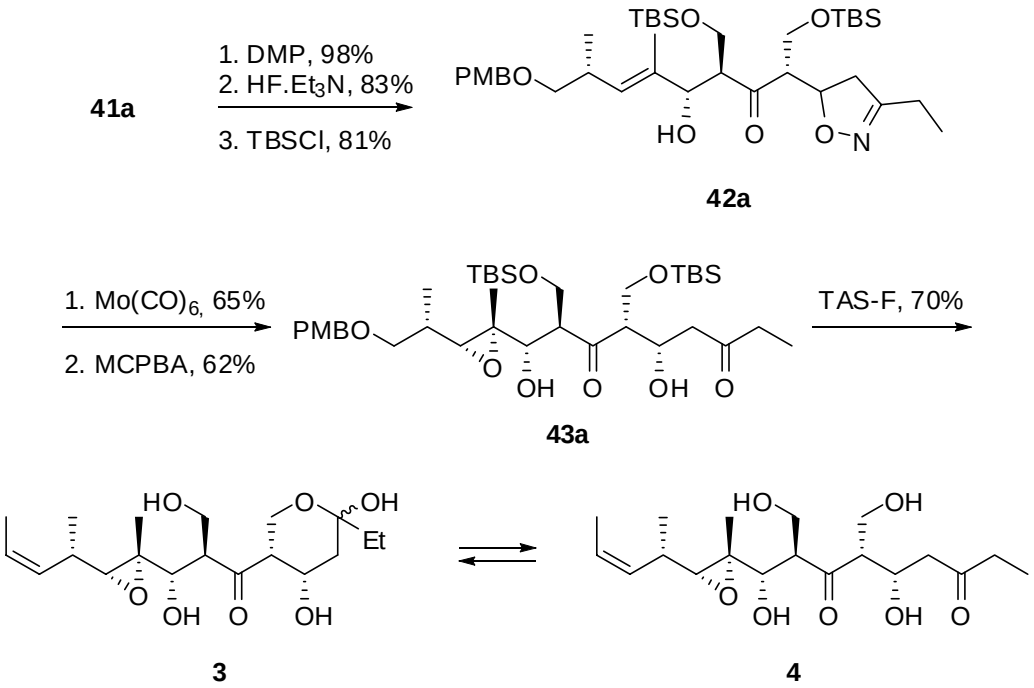
Regioselective nitrile oxide cycloadition led to the formation of isoxazoline **40** as an inseparable mixture of diastereomers. Removal of the PMB protecting group was

followed by oxidation to the aldehyde and olefination to give **41a** and **41b** (Scheme 12).



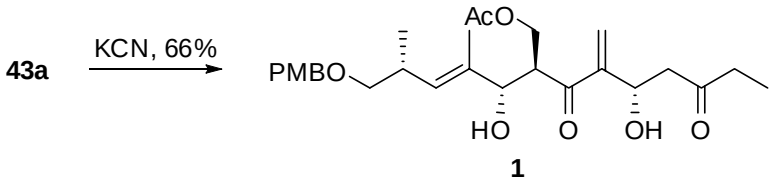
Scheme 12

The less polar diastereomer, **41a,** was converted into myriaporones 3 and 4 (**3-4)** by the sequence outlined in Scheme 13. DMP was used to oxidize the secondary hydroxy group to the corresponding ketone. Subsequent global silyl deprotection and reprotection provided **42a**. Reduction of the isoxazoline group with $Mo(CO)_6$ and epoxidation gave **43a**. Finally, deprotection of the primary alcohols with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) resulted in the formation of myriaporone 4 (**4**) as an equilibrium mixture with myriaporone 3 (**3**) (Scheme 13).



Scheme 13

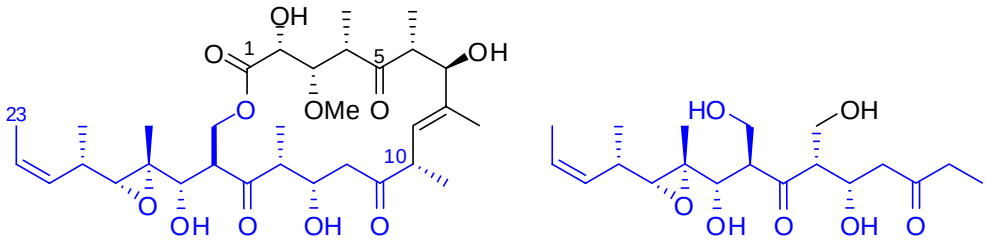
The use of acetate protecting groups instead of TBS ethers led to an unexpected reaction (Scheme 14). An attempted mild deprotection of **43a** induced selective elimination to form myriaporone **1**.



Scheme 14

6. Synthesis of C10-C23 region of tedanolide

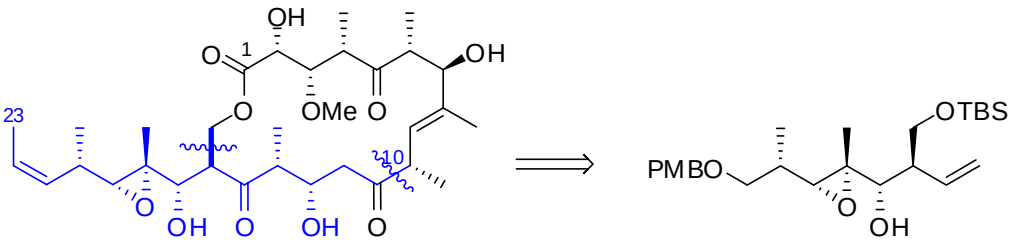
In this section we summarize the synthesis of tedanolide (**5**) with a focuse on the C10-C23 region, which is similar to the myriaporone 4 (**4**) (Figure 8)



5 **4**

Figure 8

The synthesis reported by Taylor[23,24] explained in the previous section (see Schemes 1-2) is one of the more interesting approaches for C10-C23 tedanolide fragment. The commomn intermediate **11a** for the synthesis of tedanolides (**5-7**) and myriaporones (**1** and **4**) is shown in Figure 9.

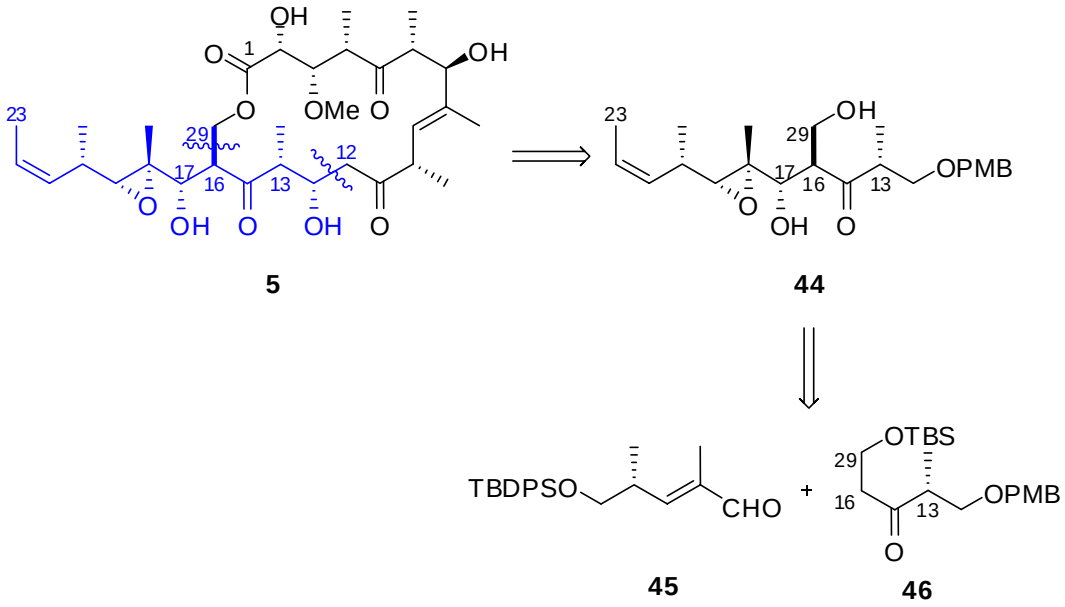


5 **11a**

Figure 9

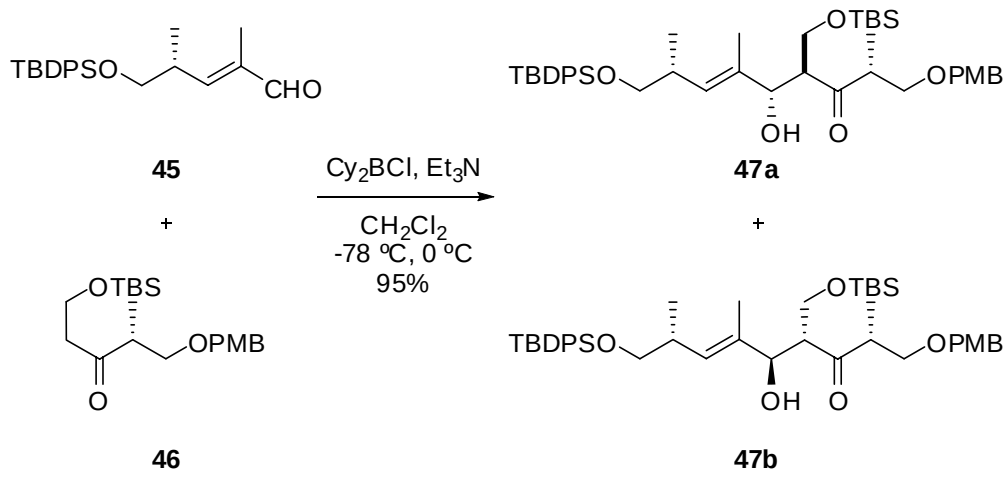
Loh *et al.*[32] proposed a synthesis of this fragment using a boron-mediated aldol reaction as the key step to control the configuration of the new stereocenters. The retrosynthetic plan for this approach is shown in Scheme 15.

32 Loh, T.-P.; Feng, L.-H. *Tetrahedron Lett.* **2001**, *42*, 3223-3226.



Scheme 15

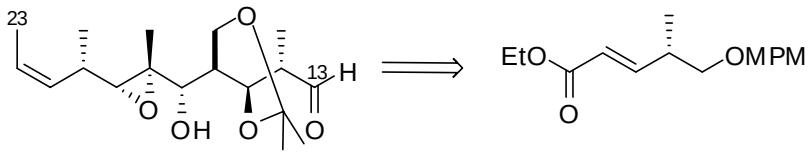
Aldehyde **45** was synthesized from commercially available methyl *(S)*-3-hydroxy-2-methylpropionate.[33] With the two fragments, **45** and **46,** a boron-mediated aldol reaction using Paterson's conditions[33] proceeded smoothly to give as a 9:1 mixture of separable diastereomers, **47a** (major) and **47b** (minor) in 95% yield (Scheme 16).



33 Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182-4184.

Scheme 16

In the approach reported by Miyashita[34] a higher diastereoselective synthesis of subunit C13-C23 (**48**) of tedanolide is described. The procedure involved two stereoselective epoxidations of regioisomeric trisubstituted double bonds and a stereospecific S_N2' methylation reaction of a *trans-γ,δ*-epoxy-*cis-α,β*-unsaturated ester as the key steps. The starting material of the synthesis is the ester **49** shown in Scheme 17.



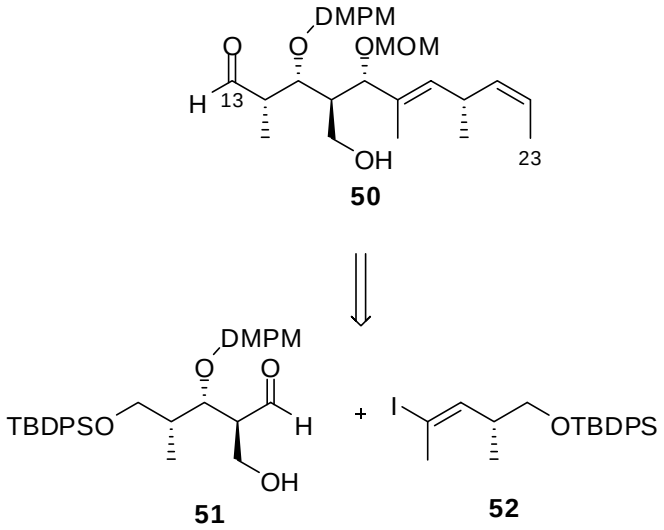
48 **49**

Scheme 17

The synthesis of fragment **50** by Yonemitsu *et al.*[35] with the 3,4-dimethoxybenzyl protecting group (DMPM) results from the coupling of fragments C13-C17 (**51**) and C18-C21 (**52**) (Scheme 18).

34 Iwata, Y.; Tanino, K.; Miyashita, M. *Org. Lett.* **2005**, *7*, 2341-2344.

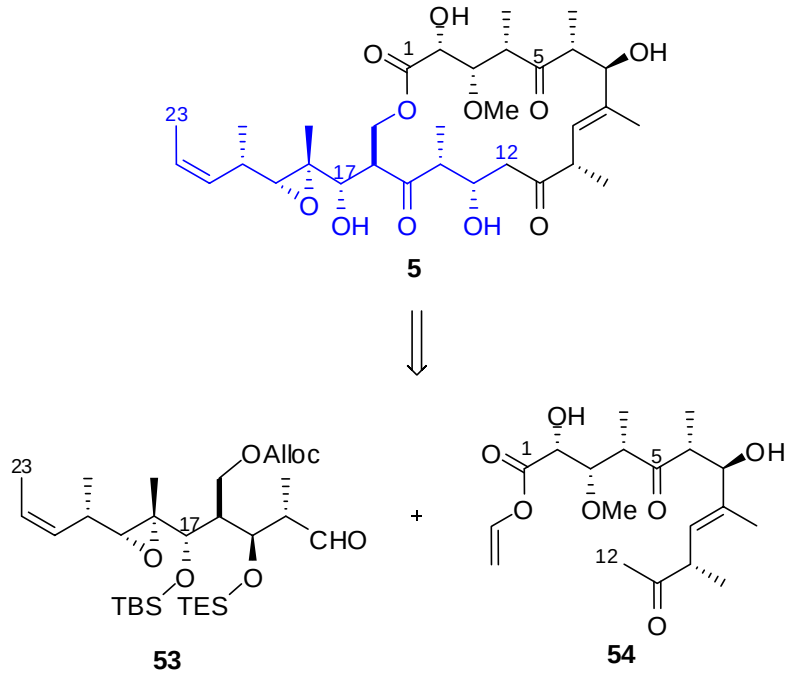
35 (a) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385-388. (b) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335-1336.



Scheme 18

The key step for the synthesis tedanolide **5** carried out by Roush[36] is a stereoselective methyl ketone aldol reaction of aldehyde **53** and ketone **54** (Scheme 19). They chose to protect the C16 hydroxymethyl group of **53** as an allyl carbonate (Alloc) and the C1 acid of **54** as an allyl ester, to deprotect them simultaneously prior to macrolactonization.

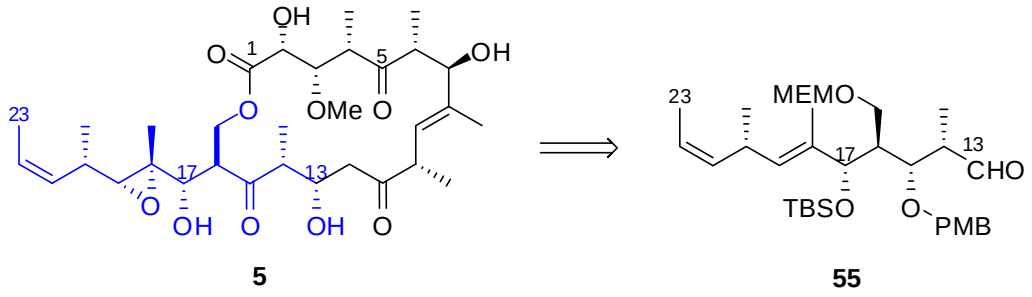
36 (a) Roush, W. R.; Lane, G. C. *Og. Lett.* **1999**, *1*, 95-98. (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. J. *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049.



Scheme 19

A recent synthesis of the C13-C23 segment of tedanolide was described by Kalesse[37] making use of orthogonal protecting groups in the construction of the carbon skeleton of **55** (Scheme 20), allowing a selective deprotection of hydroxyl groups at the end. Kalesse decided to perform the epoxidation as one of the latest steps in the synthesis. Additionally, he protected the hydroxyl groups at C17 as a TBS ether and at C15 as a PMB ether, respectively. In order to find the optimal protecting group for the primary alcohol he established a route that could be used for introducing the MOM, MEM or SEM protecting groups. The correct choice of this protecting group is key for the success of the synthesis.

37 (a) Erlich, G.; Hassfeld, J.; Eggert, U. M Kalesse, M. *J. Am. Chem. Soc.* **2006**, *128*, 14038-14039. (b) Kalesse, M.; Ehrlich, G. *Synlett* **2005**, *4*, 655-657.



Scheme 20

7. Synthesis of the C10-C23 region of 1,3-deoxytedanolide

There are also some works based on the synthesis of 1,3-deoxytedanolide **8**. As in the previous section we comment briefly the synthesis of the C10-C23 region of this molecule (Figure 10).

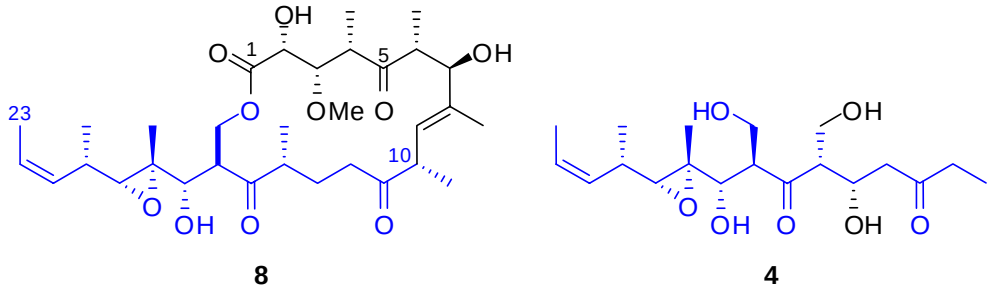
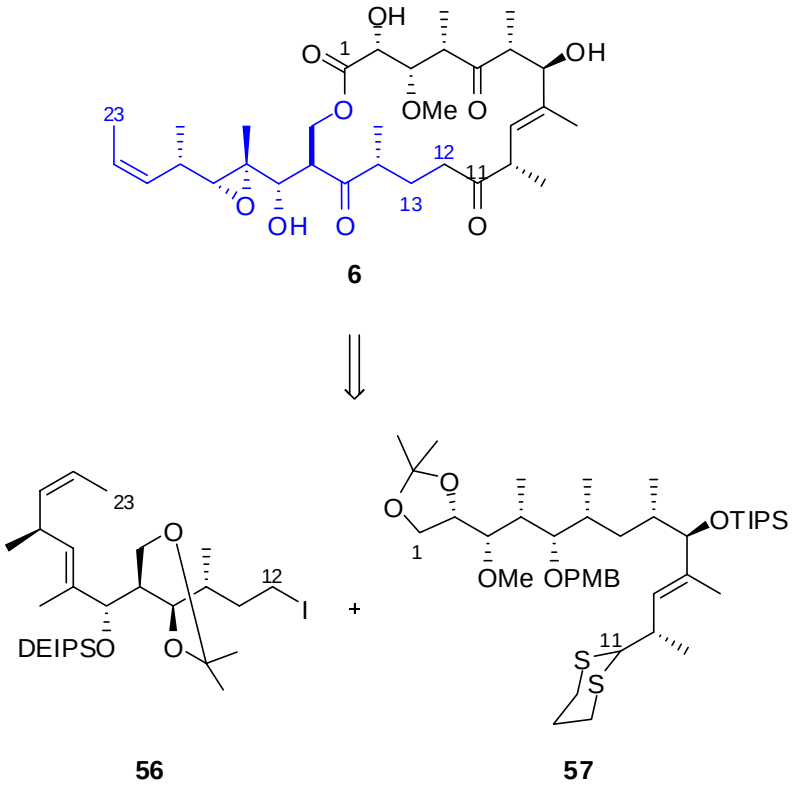


Figure 10

The synthetic plan for the synthesis of the (+)-13-deoxytedanolide (**8**) reported by Smith[38] is outlined in Scheme 21. The group recently reported a convergent total synthesis of tedanolide **7**, based in the same retrosynthetic plan.[39] Which comprise a dithiane union followed by an Evans-Tischemko reaction. The oxirane ring was introduced at the end of the synthesis.

38 (a) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350-351. (b) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042-12047.

39 Smith, A. B., III; Lee, D. *J. Am. Chem. Soc.* **2007**, *129*, 10957-10962.



Scheme 21

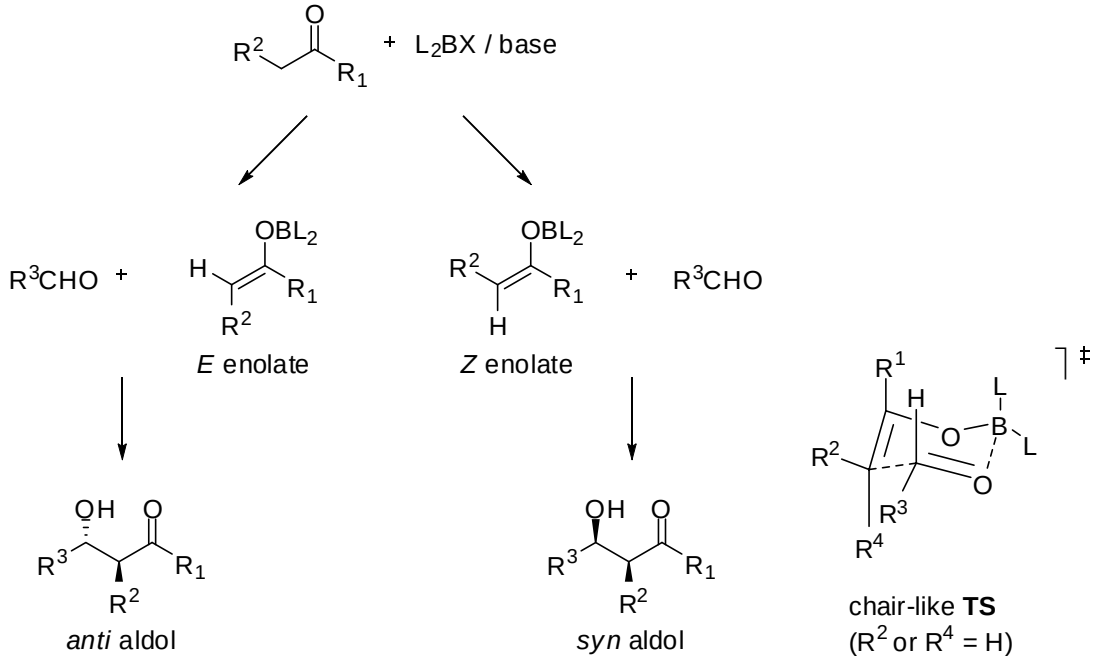
8. Aldol reactions with boron enolates.

Aldol reaction is one of the best general methods for the stereocontrolled construction of C-C bonds.[40] Therefore, the reaction has been studied in great detail. Among the many enolate types investigated, boron enolates have proved to be particulary interesting because their good reactivity and excellent stereoselectivity.[41]

40 (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1-115. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203-331. (c) Evans, D. A. Asymmetric Synthesis; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp. 1-110. (d) Heathcock, C. H. Asymmetric Synthesis; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp. 111-212. (e) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99-111. (f) Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1993; Vol. 2. (g) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317-338. (h) Braun, M. HoubenWeyl's Methods of Organic Chemistry, Stereoselective Synthesis; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1996; Vol. 3, pp. 1603-1666, also pp. 1713-1735.

41 Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1-200.

The stereoselectivity of the reaction has been accounted asuming that the aldol addition takes place through a cyclic chair-like transition state[42,43] in which the boron atom bonded to the enolate and aldehyde oxygen atoms (Scheme 22). The comparatively short boron-oxygen bonds give rise to a compact arrangement which maximizes the stereoselectivity. In agreement with this mechanistic view, *Z* enol borinates give rise to syn aldols while *E* enolborinates are precursors of anti aldols. Therefore, controlling the *E*/*Z* configuration of the enolate good stereoselectivities are observed.



Scheme 22

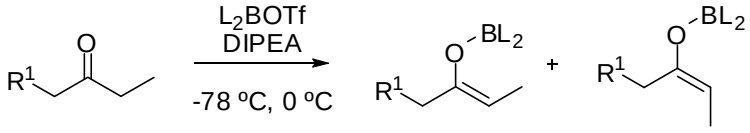
Several methodologies have been developed to achieve this stereochemical control. For instance, the stereoselective formation of *syn* aldols via *Z* enolates can be performed with boron triflate reagents L_2BOTf (L = alkyl group) in the presence of a tertiary amine.[44]

42 Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.

43 For recent theoretical studies on boron aldol reactions, see: (a) Li, Y.; PaddonRow, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481-493. (b) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471-3484. (c) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685-696.

44 Mukaiyama, T.; Inoue, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174-178.

The first studies on the effect of the substrate and the Lewis acid in the enolization under kinetic conditions of ethyl ketones with L_2BOTf and DIPEA were described by Evans.[45] The most important results are summarized in Scheme 23.



Entry	L	R^1	*Z* enolate	*E* enolate
1	*n*-Bu	Et	>97	<3
2		*i*Pr	45	55
3		*t*Bu	25	75
4	*c*-C_5H_9	Et	82	18
5		*i*Pr	19	81

Scheme 23

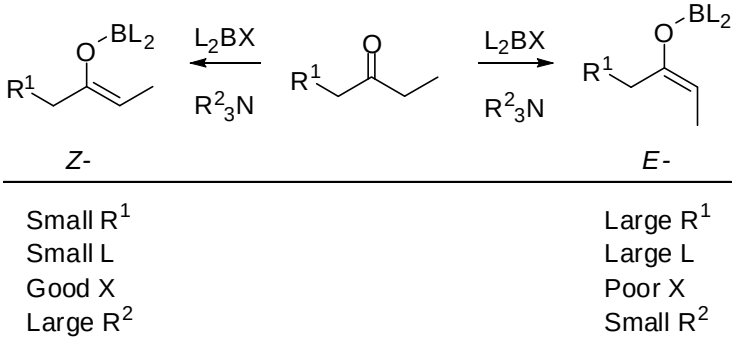
The study showed that the steric hindrance of the L and R^1 have a decisive importance in the selectivity of the enolization. With bulky L and R^1, *E* enolates were selectively obtained (entries 3 and 5 of the table in Scheme 23).

On the other hand, Brown et al. reported a study of enolizations of ethyl ketones with a wide range of Lewis acids of general formula L_2BX[46] (Scheme 24). In this study, Brown concluded that when X is a good leaving group, such as, -OTf, the *Z* enolate is formed, and when the leaving group is poor, such as –Cl, the *E* enolate is

45 Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc,* **1979**, *101*, 6120-6123.

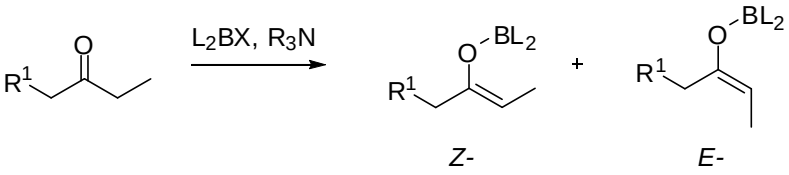
46 (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiajaran, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441-3442. (b) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram B. *J. Org, Chem.* **1992**, *57*, 499-504. (c) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram B. *J. Org, Chem.* **1992**, *57*, 2716-2721. (d) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org, Chem.* **1992**, *57*, 3767-3772. (e) Brown, H. C.; Ganesan, K. *J. Org, Chem.* **1993**, *58*, 7162-7169.

favored. Whith less hindered L and bases, the preferred enolate has the *E* configuration. The *E* enolate is also favored in apolar solvents and at low concentration.



Scheme 24

Thus, Cy_2BCl gives *E* enolates, whereas Bu_2OTf leads to the formation of *Z* enolates (Scheme 25).[47]

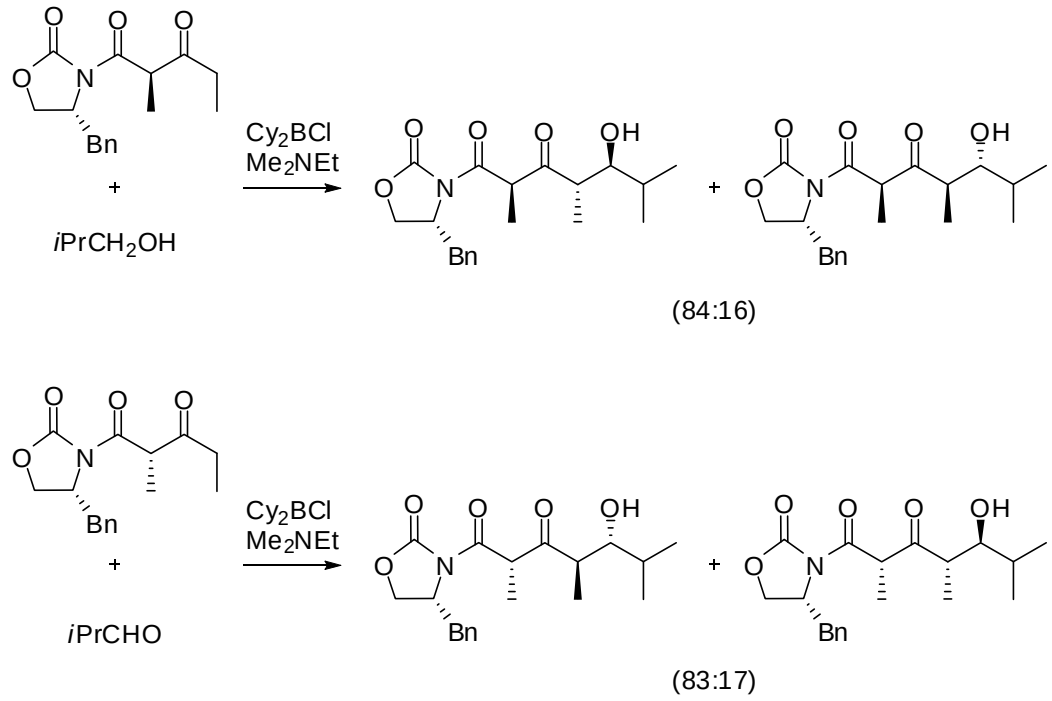


Entry	R^1	X	L	R_3N	*Z*-	*E*-
1	Et	Cl	Cy	Et_3N	21	79
2	*i*Bu	Cl	Cy	Et_3N	12	88
3	*i*Pr, Ph	Cl	Cy	Et_3N	<3	>97
4	Et	OTf	Bu	DIPEA	>97	<3
5	*i*Bu	OTf	Bu	DIPEA	>97	<3
6	Ph	OTf	Bu	DIPEA	>99	<1

Scheme 25

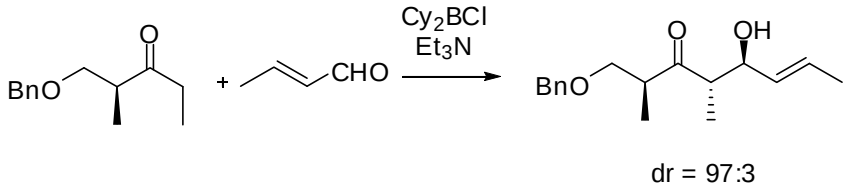
47 Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc,* **1979**, *101*, 6120-6123.

The *E* boron enolates react with aldehydes to give *anti* aldols. Thus, Evans[29] obtained *E* enolborinates with good diastereomeric ratios (Scheme 26).



Scheme 26

Paterson[48] also used the same conditions to obtain *anti* aldols with excellent diastereoselectivity with chiral ethyl ketones (Scheme 27)

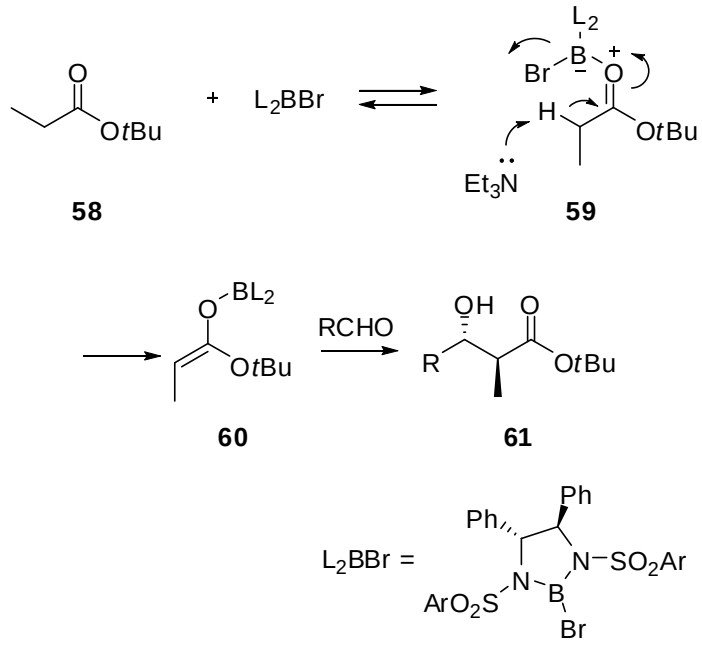


Scheme 27

One of the first models to explain the stereoselectivity of the reactions with chiral enolborinates esters and tioesters was proposed by Corey.[49] He established that *tert*-buthylpropanoate enolate **60** obtained with diazaborilidine/Et_3N (Scheme 28), reacts

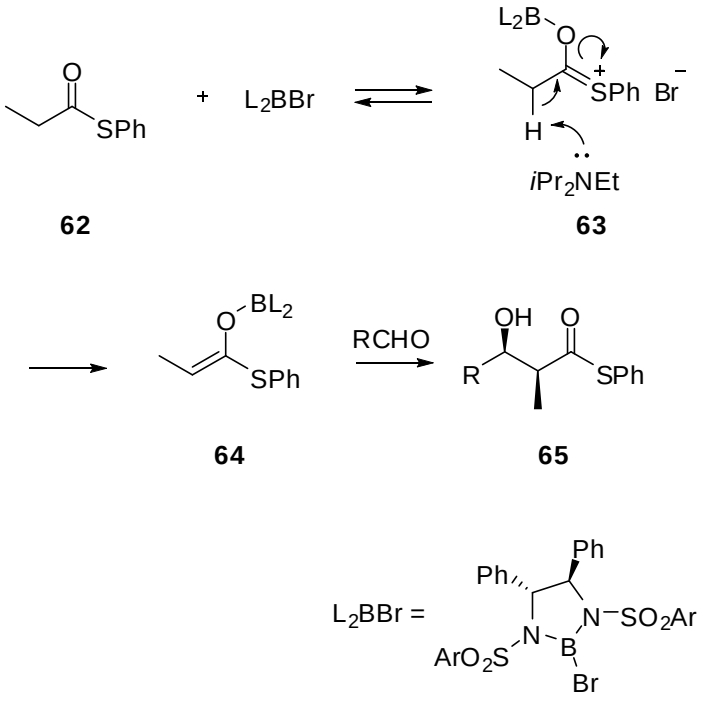
48 Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121-7124.
49 Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976-4977.

with aldehydes to give the corresponding *anti* aldols **61**, which indicates that the reaction takes place via *E* enolates. Considering that these processes are not affected by solvent polarity, an E2 mechanism was proposed.



Scheme 28

On the other hand, the enolization of *S*-phenylthiopropionate **62** with the same oxazaborolidine used before and diisopropyethylamine (DIPEA) as a base, gives *syn* aldols **65**. In this case an E1-type mechanism was proposed (Scheme 29). Accordingly, the enolate is generated by the following steps. First, the Lewis acid-carbonyl complex suffers the loss of bromide promoted by sulfur atom. In a second step, deprotonation occurs with the bulky DIPEA.



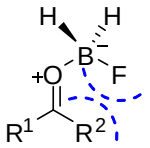
Scheme 29

These results are obtained in a polar solvent (e.g. CH_2Cl_2), but if the reaction is performed under apolar conditions (e.g. 1:2 toluene-hexane) and with less hindered bases (e.g. Et_3N), the diastereoselectivity diminishes drastically because the polar intermediate is not favored.

These mechanistic proposals also explain the results previously described by Brown for enolizations with L_2BOTf, which evolves via an E1 mechanism because the triflate is a good leaving group, while L_2BCl as Lewis acids favors an E2 mechanism.

Paterson and Goodman proposed a mechanism supported by *ab initio* calculations to explain the formation of the complex between aldehydes and ketones with H_2BF.[50] Accordingly to these calculation, the most stable conformation of the complex ketone-BH_2F is that in which the B-F bond eclipses the ketone C=O double bond (Figure 11).

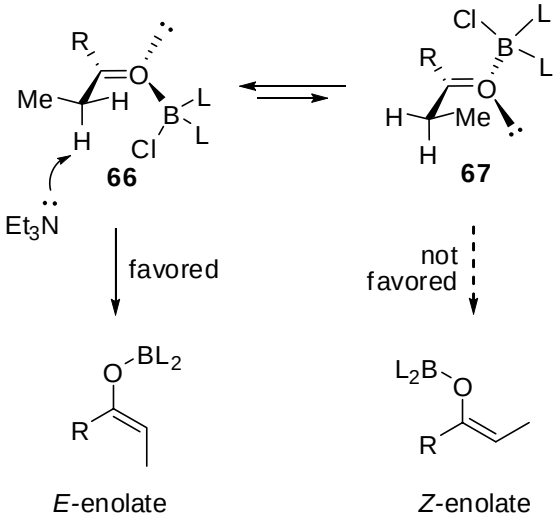
50 Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1992**, *33*, 7219-7222.



$R^1 > R^2$

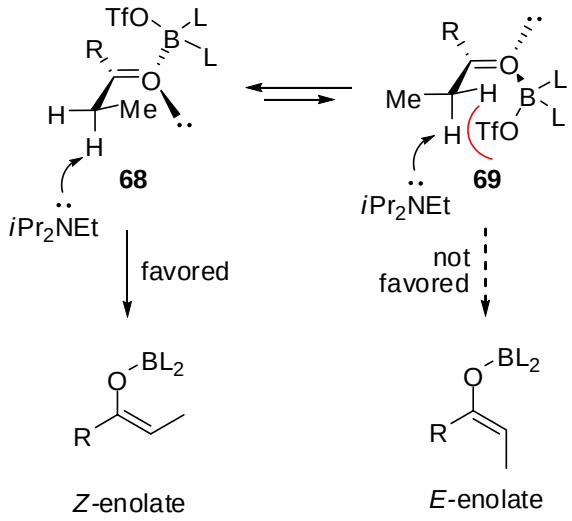
Figure 11

For L_2BCl it was concluded that if complex **66** (Scheme 30) is favored, the methyl group will be perpendicular to the carbonyl group and, with a less hindered amine, the abstraction of the H α to the carbonyl will lead to the enolate with the *E* configuration.



Scheme 30

For L_2BOTf mediated reactions, it is the steric hindrance which determines the enolate geometry. Considering both possible complexes when the Lewis acid is coordinated to the carbonyl, the preferred enolate **68** is the one which results from the approach in which the base finds less steric hindrance (Scheme 31).



Scheme 31

More recently other calculations on boron-mediated aldol reactions have been reported by the group of Marco and Carda.[51] This group reported a study of 3-pentanone enolization with triethylamine and several L_2BCl Lewis acids, where L can be H, Me or *i*Pr groups. They arrived to the same conclusion as Paterson and Goodman (Figure 12).

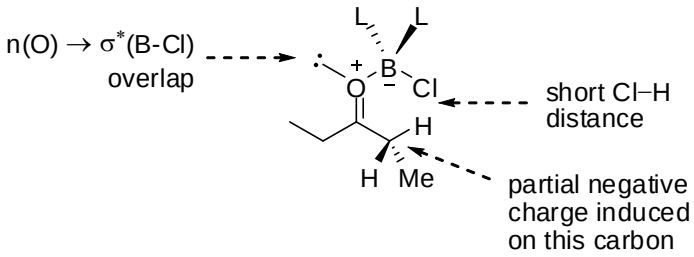


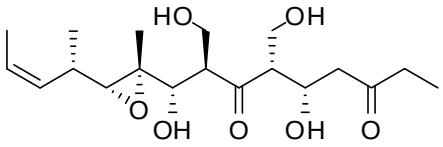
Figure 12

This study established that for less bulky ligands (L) the *Z* enolates are favored while, for bulky ligands, *E* enolates are preferred.

51 Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2001**, *57*, 6239-6247.

OBJECTIVES

Only two synthesis of **1**[1] have been developed up to date, which proceed by a linear approach. Therefore, we set as a goal to accomplish a first convergent synthesis of **1** (figure 1).



1

Figure 1

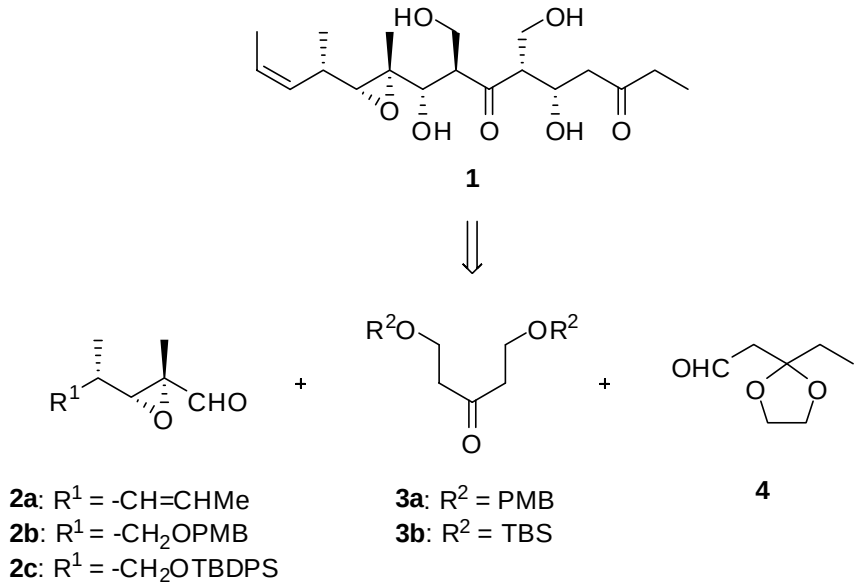
This modular approach would allow the obtention of new derivatives of **1** for their biological evaluation. With this purpose, and in collaboration with PharmaMar, we embarked in the total synthesis of **1** and derivatives.

1 (a) Hines, J.; Roy, M.; Cheng, H.; Agapakis, C. M.; Taylor, R.; Crews, C. M. *Mol. Biosys.* **2006,** *2*, 371-379. (b) Fleming, K. N.; Taylor, R. E. *Angew. Chem., Int. Ed*. **2004**, *43*, 1728-1730. (c) Perez, M.; del Pozo, C.; Reyes, F.; Rodriguez, A.; Francesch, A.; Echavarren, A. M.; Cuevas, C. *Angew. Chem., Int. Ed*. **2004**, *43*, 1724-1727. (d) Perez, M.; del Pozo, C.; Francesch, A.; Cuevas, C. WO2004011458 A1. (e) Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Org. Lett*. **2002**, *4*, 2953-2955. (f) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Yonemitsu, O. *Chem & Pharm. Bull*. **2000**, *48*, 1761-1765. (g) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Kusaka, S.-I.; Matsui, K.; Yonemitsu, O. *Tetrahedron. Lett* **2000**, *41*, 6441-6445. (h) Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Tetrahedron. Lett.* **1998**, *39*, 9361-9364

RESULTS

1. Retrosynthetic analysis and strategies

Our retrosynthetic plan designed to synthesize myriaporone 4 (**1**) is outlined in Scheme 1.

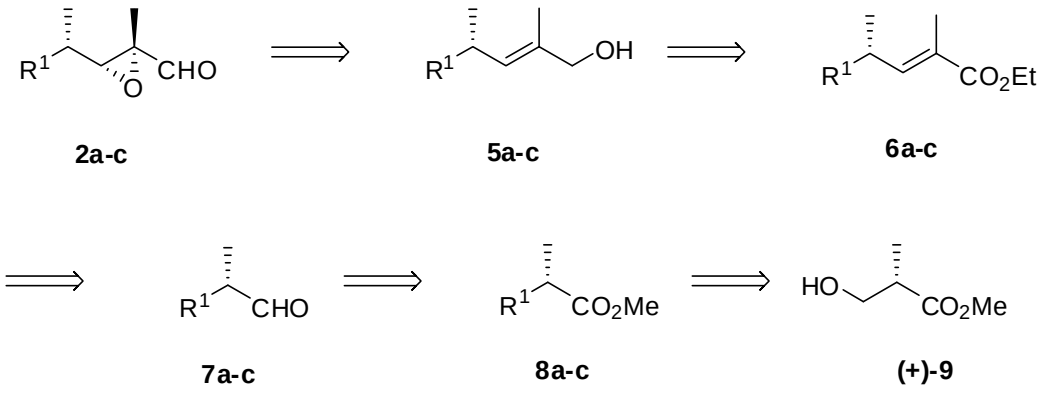


Scheme 1

The retrosynthesis hinges upon the three fold disconnection of **1** in two aldehydes (**2a, 2b** or **2c** and **4**) and a ketone (**3a** or **3b**), which could be assembled using two

stereoselective aldol reactions,[1] one with an *anti*[2] relative stereochemistry and another *syn*.[3]

For the construction of the left-hand aldehydes **2a-c**, two different synthetic plans were devised (Scheme *2*). On the one hand, for the synthesis of the **a** series, the *Z*-double bond would be introduced in the early stages. On the other hand, in the **b** and **c** series a protected alcohol was used as an equivalent of the double bond, which would be built after the assembly of the fragments. We chose two different protections of the alcohol: the *p*-methoxybenzyl group (PMB) (allowing for chelation on the oxygen atom) and the bulkier, non-chelating *tert*-butyldiphenylsilyl group (TBDPS).



a: R^1 = -CH=CHMe, **b:** R^1 = -CH_2OPMB and **c:** R^1 = -CH_2OTBDPS

Scheme 2

We focused on the allylic alcohol scaffold embedded on the structure of **2** so that it could be generated from **5** by an asymmetric epoxidation followed by a Swern oxidation[4] to furnish the desired aldehyde. In turn, **5** derives from the α,β-unsaturated ester **6** resulting from the olefination of aldehyde **7**, which could be obtained from the ester **8** by functional group interconversion. Esters **8b** and **8c** could derive from readily

1 (a) Reiser, O.; Mengel, A. *Chem. Rev*. **1999**, *99*, 1191.(b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1-76

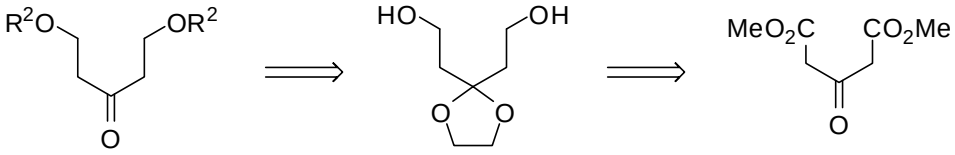
2 a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747-5750. b) Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213-1214. c) Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T.-H. *J. Org. Chem.***1996**, *61*, 2038-2043.

3 Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586-2587.

4 Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165-185.

available Roche's ester **(+)-9** by simple protection with the appropriate reagents, whereas **8a** would be achieved from this same ester by oxidation and *Z*-selective Wittig-type olefination.

The carbonyl compounds **3a** and **3b** could be obtained from acetal **10**. Acetal **10** could be prepared from **11** by acetalization followed by reduction of the diester to the diol (Scheme 3).

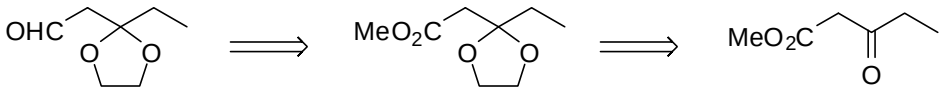


3a (R^2= PMB)
3b (R^2= TBS)

10 **11**

Scheme 3

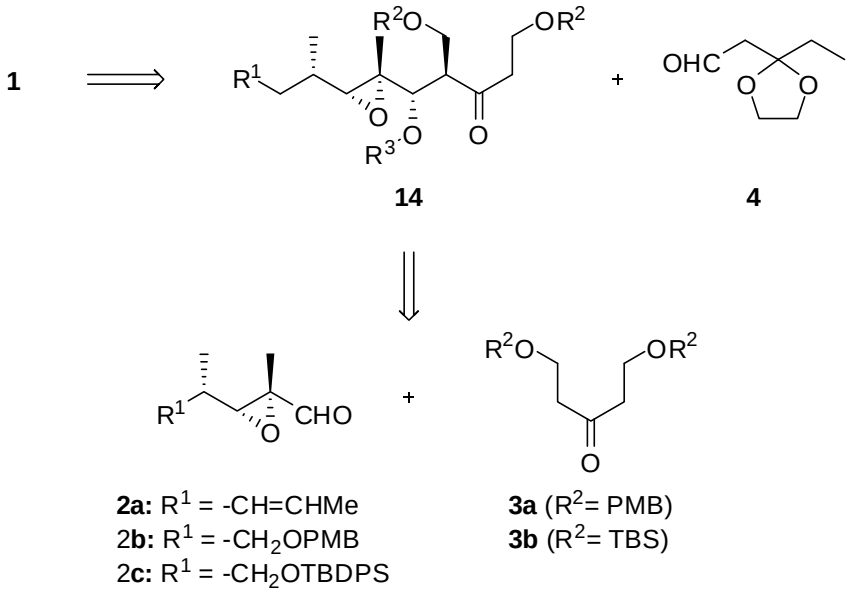
Finally, the right-hand aldehyde **4** posed less problems due to the minor level of complexity. We planned to prepare **4** by reduction of **12**, which can be obtained from **13** as shown in Scheme 4.



4 **12** **13**

Scheme 4

The planned coupling of the fragments is outlined in Scheme 5. We decided to exploit the chiral information of the aldehyde **2**, relying on a substrate controlled stereoselective aldol reaction. Then, the second aldol reaction between fragment **14** and aldehyde **4** would be again substrate controlled. Therefore, our synthetic plan hinged on the transmission of the stereochemical information of the aldehyde **2** to the myriaporone backbone via the coupled fragment **14**.



Scheme 5

In summary, we designed our synthesis so that all the chiral information embedded in the myriaporone backbone emanates from the configuraton of aldehyde **2**. Our plan, then, intended to avoid the use of other elements of chiral induction such as ligands or auxiliaries.

2. Synthesis of central ketone

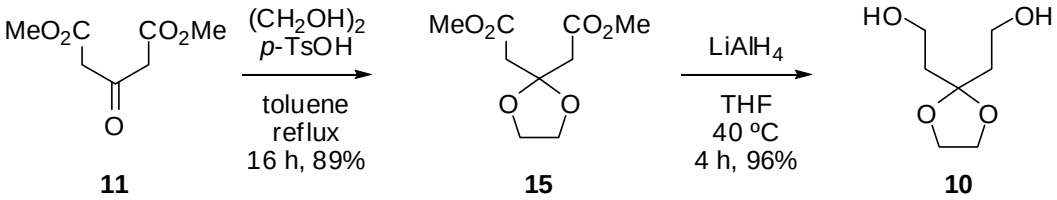
2.1. Synthesis of ketone 3a

We began the synthesis of ketone **3a** using the methodology described by Reagan and Davenport.[5] Dimethyl acetonedicarboxylate **11** was chosen as the starting material for the preparation of ketone **3a**. The ethylene acetal **15** was prepared in a conventional manner[6] (

Scheme *6*), and the two ester groups were then reduced to primary alcohols using $LiAlH_4$ to give diol **10** in good yield (85% in two steps).

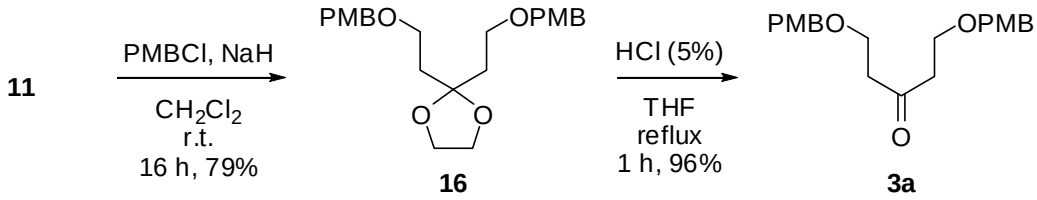
5 (a) Davenport, R. J.; Regan, A. C. *Tetrahedron Lett.* **2000**, *41*, 7619-7622. (b) Yadav. J. S.; Bandyopadhyay, A.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 4907-4911.

6 Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, **1999**, 308-322, 724-727.



Scheme 6

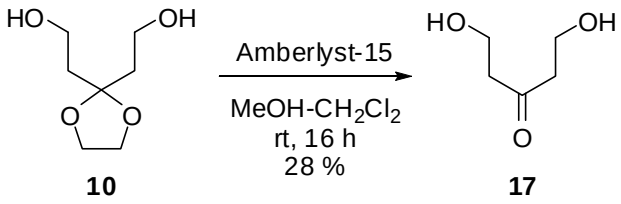
The next step was the protection of both hydroxyl groups of **10** as PMB ethers with NaH and PMBCl, to furnish compound **16** in good yield. Finally, the desired ketone **3a** was obtained by hydrolysis of acetal **16** with aqueous HCl (Scheme 7).



Scheme 7

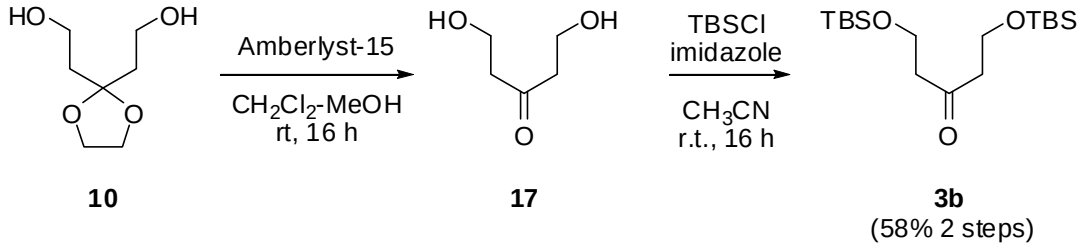
2.2. Synthesis of ketone 3b

The synthesis of central ketone **3b** was very similar to the *p*-methoxybenzyl protected one (**3a**, Scheme 6). We cleaved the acetal protecting group of **10** using Amberlyst-15 in MeOH-CH_2Cl_2 to give dihydroxyketone **17**. Nevertheless, the yield was poor because the compound was very difficult to handle due to its water solubility. For that reason we decided to avoid the isolation of **17** and attempt to postpone the purification step until both hydroxyl groups would be protected (Scheme 8).



Scheme 8

After much experimentation we found that the best procedure to obtain **17** was filtering the Amberlyst-15 resin off, concentrating the crude to dryness and directly submitting it to the protection reaction of the hydroxyl groups as TBS ethers.[7] Ketone **3b** was obtained in 50% yield (2 steps) (Scheme 9).

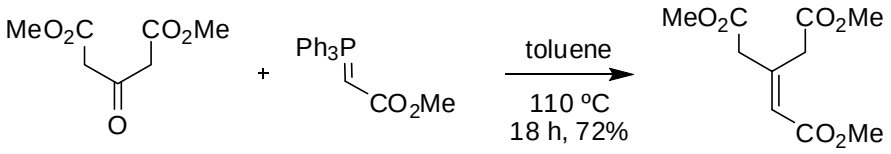


10 **17** **3b** (58% 2 steps)

Scheme 9

2.3. Alternative synthesis of ketone 3b

Alternatively, while the improval of the synthesis described above was carried on, a new strategy was envisioned in which the key step was an ozonolysis. Thus, a Wittig reaction was performed between **11** and the commercially available phosphonium salt **18** to give the alkene **19** in 72% yield (Scheme 10).

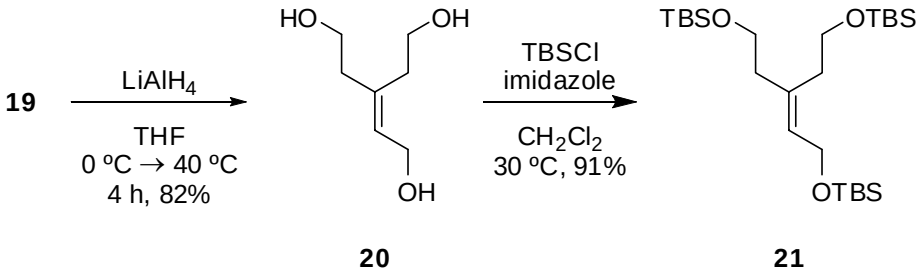


11 **18** **19**

Scheme 10

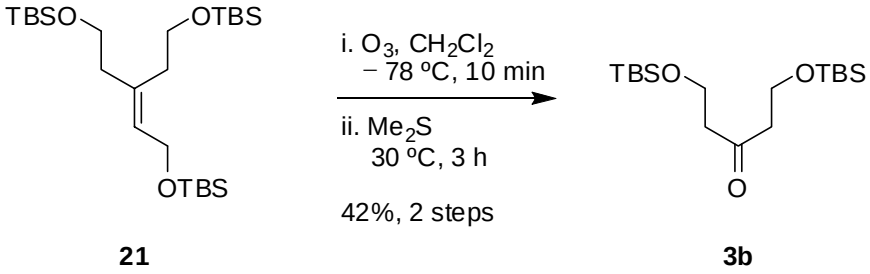
The triester **19** was reduced to triol **20** using $LiAlH_4$. Protection of the alcohols of **20** as TBS ethers gave **21** in a 54% yield in three steps (Scheme 11).

7 Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.



Scheme 11

Finally, the ozonolysis of compound **21** was carried out at low temperature to afford the desired ketone **3b** with 23% overall yield (Scheme 12).

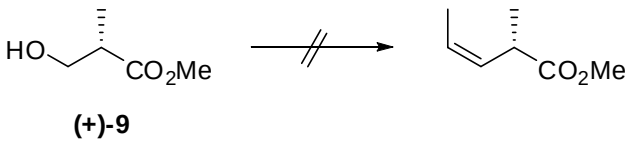


Scheme 12

3. Synthesis of left side aldehydes

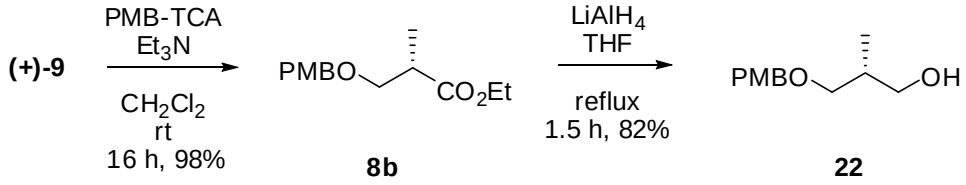
3.1. Synthesis of aldehyde 2a

As it has been shown in Scheme 2 of the retrosynthesis, our first effort in the synthesis of **2a** was to introduce the *Z*-double bond directly after the oxidation of alcohol **(+)-9** to aldehyde (Scheme 13). However this route failed, probably due to the lability of the intermediate β-aldehyde ester, so another path had to be developed.



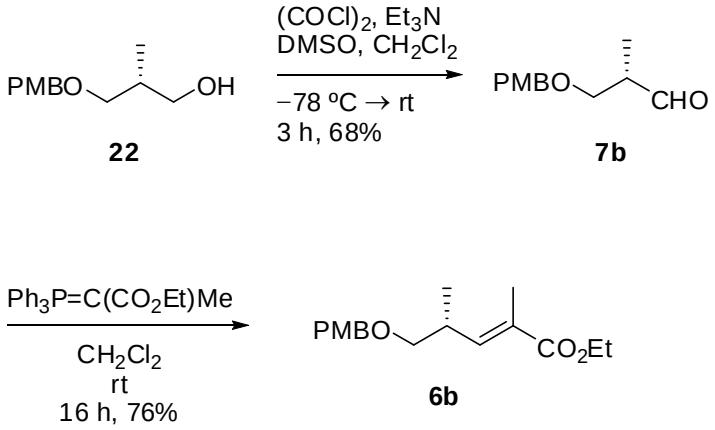
Scheme 13

The new strategy started with the protection of the hydroxyl group of alcohol **(+)-9** as the PMB ether using the readily prepared PMB-TCA reagent.[8] Subsequently, by reduction of the ester function in **8b** with $LiAlH_4$, alcohol **22** was obtained in 80% yield in two steps (Scheme 14).



Scheme 14

A Swern oxidation[9] of **22** and a Wittig olefination of the resulting aldehyde lead to the α,β-insaturated ester **6b** (52% yield, 2 steps) (Scheme 15).

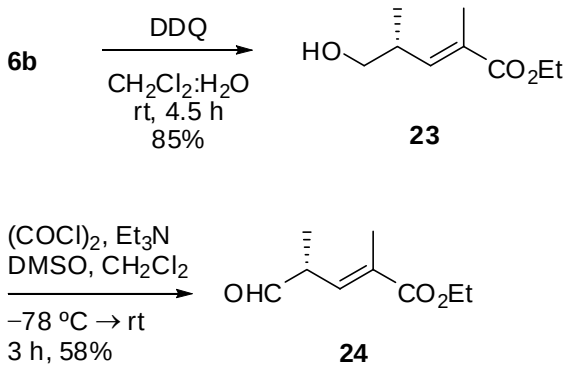


Scheme 15

Then, oxidative cleavage of the PMB protecting group was performed using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in aqueous CH_2Cl_2 to give alcohol **23** (Scheme 16), which was oxidized to aldehyde **24** following the Swern oxidation protocol (49% yield in two steps).

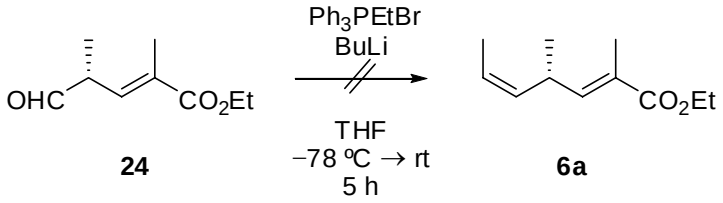
8 Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481-1484.

9 (a) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979,** *44*, 4148-4150. (b) Omura, K.; Swern, D. *Tetrahedron* **1978,** *38*, 1651-1660. (c) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J Org. Chem.* **1978,** *43*, 2480-2482.



Scheme 16

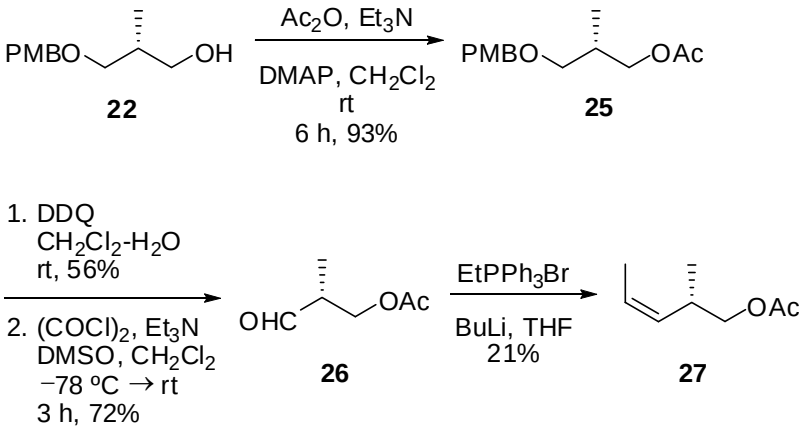
We planned to introduce the *Z*-double bond of **2a** by a Wittig olefination. However, the reaction of **24** with the commercially available ethyltriphenylphosphonium bromide failed to yield the desired product (Scheme 17). Apparently compound **24** is as labile as the aldehyde derived from hydroxyester **(+)-9** (Scheme 13).



Scheme 17

Alternatively we envisioned the possibility to introduce the *Z*-double bond in an earlier step. We started this new synthetic plan protecting alcohol **22** as acetate (Scheme 18).[10] Subsequently, the PMB protecting group of **25** was cleaved using the oxidative procedure described in Scheme 16 furnishing **26**, which was subjected to Wittig olefination to give **27** in 8% yield from **22** in four steps. The attempt to isolate the corresponding alcohol, once the acetate group of **27** was removed, failed due to its volatility.

10 Hoefle, G.; Steglich,W. *Synthesis*,**1972**, 619-621.



Scheme 18

At this point of the synthesis, Kalesse reported the synthesis of the alkene derivative of **2a** (Figure 1).[11]

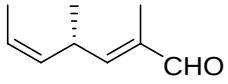
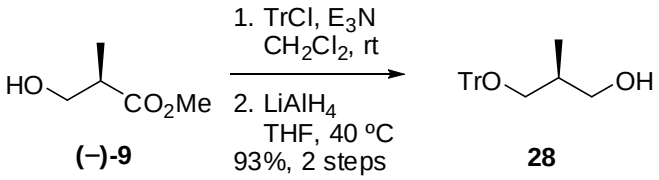


Figure 1

We followed the same strategy starting from the ester **(–)-9** by protecting the hydroxyl function with the acid labile trityl group.[12] Reduction with $LiAlH_4$ provided alcohol **28** in 93% yield (Scheme 19).



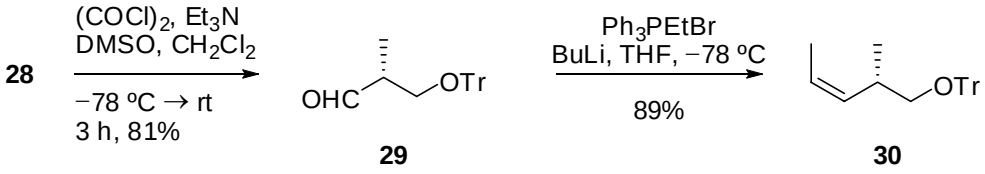
Scheme 19

Subsequently a Swern oxidation was performed furnishing aldehyde **29** in 81% yield (Scheme 20). This step was also carried out by a Parikh-Doering oxidation,[13]

11 Hassfeld, J.; Kalesse, M. *Synlett* **2002**, 2007-2010.

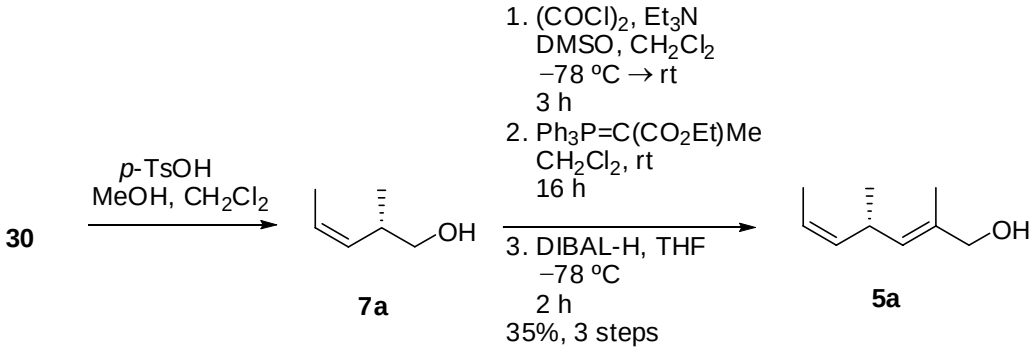
12 (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*. 2nd ed.; John Wiley & Sons: New York, **1999**; 17–292. (b) Kocienski, P. J. Protecting Groups; Georg Thieme: New York, **1994**; 21–117.

obtaining **29** in 78% yield. After an aqueous treatment, **29** was directly subjected to a Wittig olefination to form the desired *Z*-double bond. Alkene **30** was obtained as the major product of the reaction in 72% yield (95:5 *Z/E*).



Scheme 20

Removal of the trityl group using *p*-toluenesulfonic acid (*p*-TsOH) afford alcohol **7a**; which, by a sequence of Swern oxidation, Wittig olefination and reduction furnished the allylic alcohol **5a** (Scheme 21).

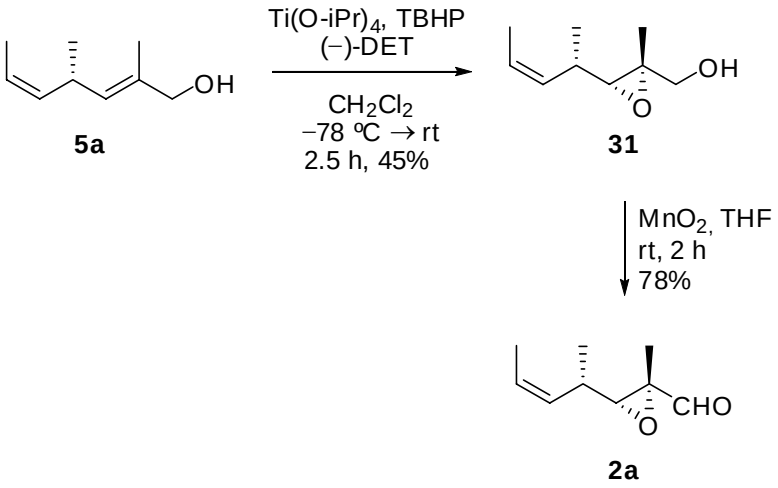


Scheme 21

In this pathway we encountered problems handling alcohol **7a** due to its volatility. To solve this problem we performed Swern oxidation and Wittig olefination without isolation aldehyde **7a**. Nevertheless, we obtained sufficient amounts of **5a** (35% from **30**) to proceed with the synthesis of the desired aldehyde **2a**.

Next we performed a Sharpless epoxidation[14] of the allylic alcohol **5a** to give the epoxyaldehyde **31** as a 10:1 mixture of diastereomers in favor of the desired one (Scheme 22).

13 Parikh, J. P.; von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.
14 Katsuki, T.; Sharpless, B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.



Scheme 22

Finally, the resulting epoxyalcohol **31** was oxidized with MnO_2 to give the desired epoxyaldehyde **2a** in an overall yield of 18% from **(–)-9**. It must be noted that for this oxidation step other procedures were successfully tested. Thus, the Swern and Parikh-Doering oxidations of **31** provided **2a** with comparable results in all cases.

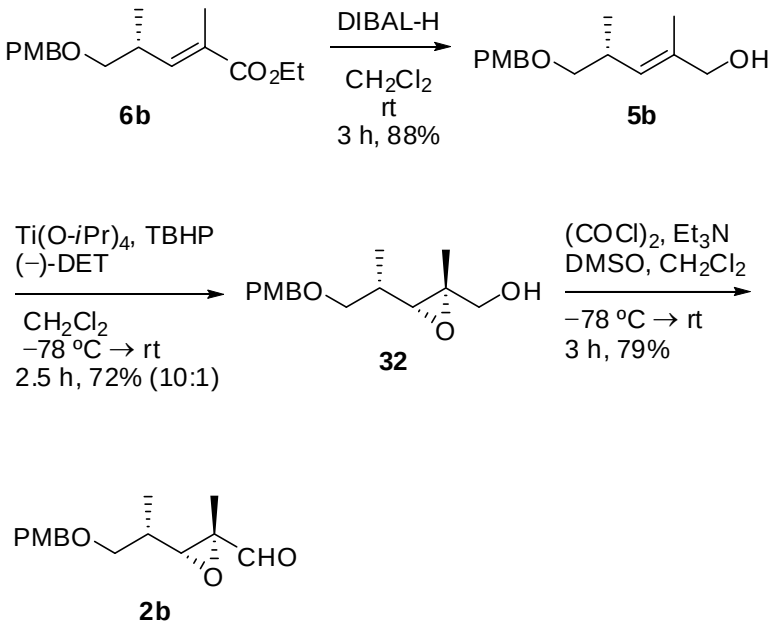
3.2. Synthesis of aldehyde 2b

Starting with the common intermediate **6b** depicted in Scheme 2 and following a similar synthesis than the one proposed by Taylor[15] and PharmaMar[16] in their respective syntheses of myriaporone 4 (**1**), the desired aldehyde **2b** was obtained. Ester **6b** was reduced with diisobutyl aluminum hydride DIBAL-H to furnished alcohol **5b** in 81% yield. Then, a Sharpless epoxidation over **5b** led to **32**[17] as a 10:1 mixture of epoxides in 72% yield. Finally, epoxyaldehyde **2b** was obtained by the Swern oxidation of the corresponding alcohol **32** in 21% overall yield from **(+)-9** (Scheme 23).

15 (a) Fleming, K. N.; Taylor, R. E. *Angew. Chem. Int. Ed.* **2004,** *43*, 1728-1730. (b) Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Org. Lett.* **2002,** *4*, 2953-2955. (c) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998,** *39*, 9361-9364.

16 Pérez, M.; del Pozo, C.; Reyes, F.; Rodríguez, A.; Francesch, A.; Echavarren, A. M.; Cuevas, C. *Angew. Chem. Int. Ed.* **2004,** *43*, 1724-1727.

17 (a) Meyers, A. I., Hudspeth, J. P. *Tetrahedron Lett.* **1981,** *22*, 3925-3928. (b) Meyers, A. I., Babiak, K. A., Campbell, A. L., Comins, D. L., Fleming, M. P., Henning, R., Heuschmann, M., Hudspedth, J. P., Kane, J. M., Rider, P. J., Roland, D. M., Shimuzu, K., Tomioka, K., Walkup, R. D. *J. Am. Chem. Soc.* **1983,** *105*, 5015-5024.

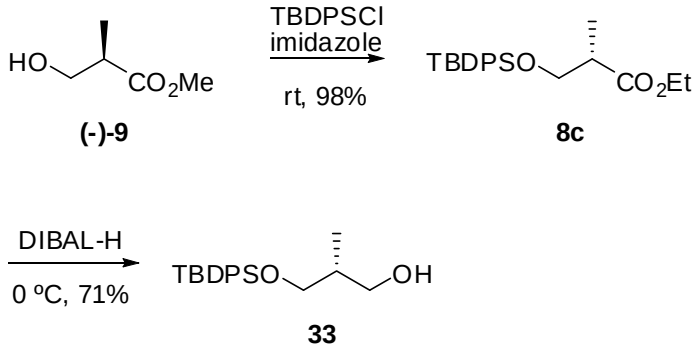


Scheme 23

3.3. Synthesis of aldehyde 2c

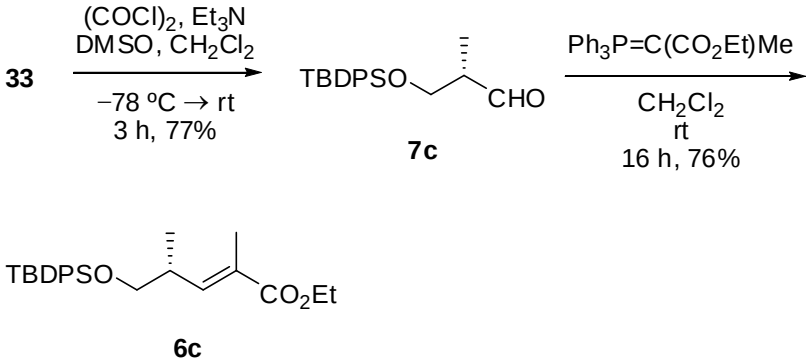
In order to establish the effect of the protecting group in the outcome of the aldol reaction, our strategy aimed for the introduction of different groups in the left side aldehyde. Thus, an analog of **2b** in which the alcohol is protected as a *tert*-butyldiphenylsilyl (TBDPS) group was prepared.

The synthesis of aldehyde **2c** followed a synthetic plan similar to the one devised for **2b**. Starting with **(+)-9**, after protection of the alcohol as the TBDPS ether, **8c** was obtained in quantitative yield. Reduction of the ester function of **8c** to the alcohol **33** was accomplished with DIBAL-H at 0 ºC (71%, Scheme 24).



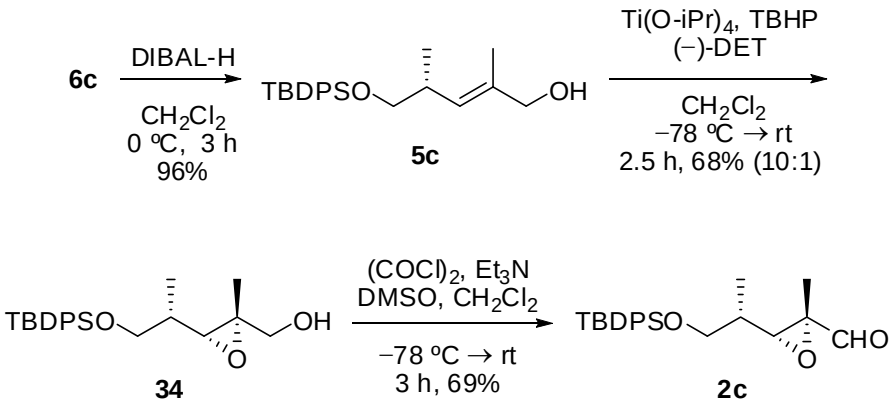
Scheme 24

A Swern oxidation and a Wittig olefination were subsequently performed to give **6c** as detailed in Scheme 25. The α,β-unsaturated ester **6c** was obtained in 59% yield from **33**.



Scheme 25

Reduction of ester **6c** with DIBAL-H afforded alcohol **5c** which was subjected to Sharpless epoxidation yielding epoxyalcohol **34** as a 10:1 mixture, favoring the desired diastereomer. Finally, Swern oxidation of **34** furnished the desired aldehyde **2c** in 28% yield (3 steps) (Scheme 26).

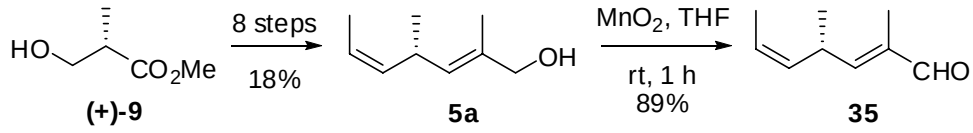


Scheme 26

3.4. Synthesis of aldehyde 35

We also synthesized new series of derivatives of left hand aldehydes without the oxirane ring. For the synthesis of these products we used the strategy reported by Kalesse *et al.*[11]

From the intermediate **5a** described above in Schemes 22 and 23, we obtained **35** by the oxidation of the primary alcohol to the aldehyde as outlined in Scheme 27. The oxidation of **5a** was performed using MnO_2 furnishing aldehyde **35** in a 16% overall yield from **(+)-9**.

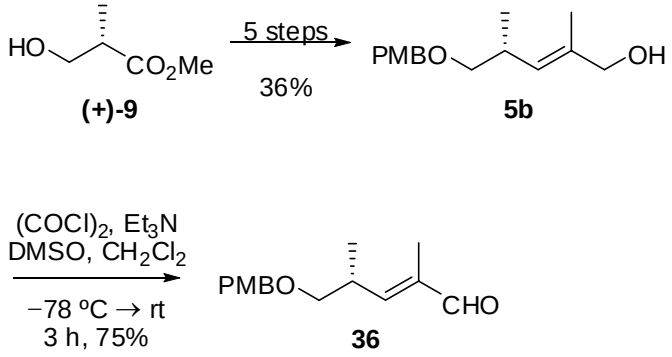


Scheme 27

3.5. Synthesis of aldehyde 36

The derivative of aldehyde **2b** without the oxirane ring was also prepared starting from allylic alcohol **5b** (Scheme 24), previously synthesized from **(+)-9** (Schemes 14

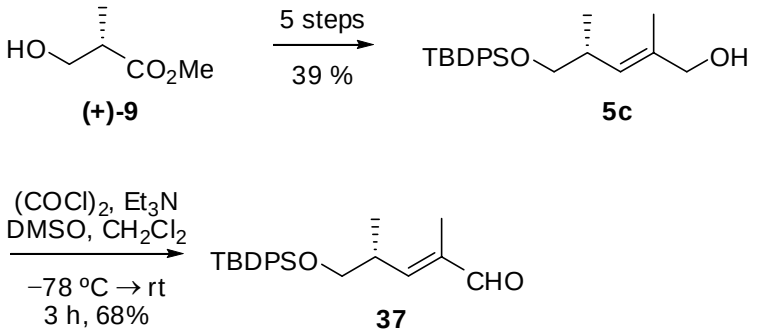
and 15). Thus, the hydroxyl group of **5b** was oxidized to aldehyde **36** by the Swern oxidation with an overall yield of 27% (six steps) (Scheme 28)



Scheme 28

3.6. Synthesis of aldehyde 37

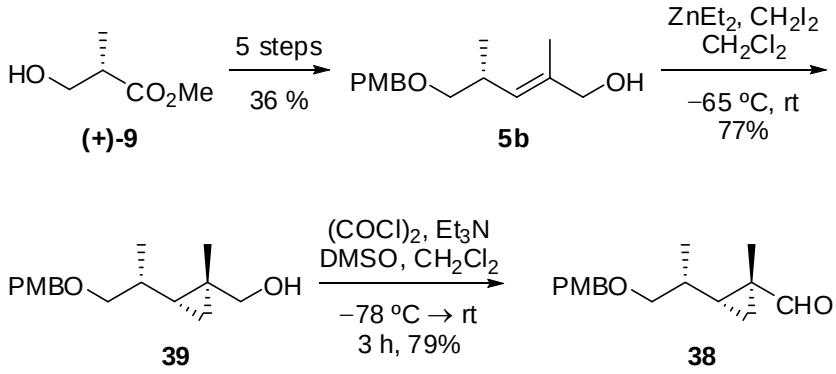
The analogue of **36** with a TBDPS protective group was also prepared. In this case, the previously synthesized allylic alcohol **5c** (Schemes 26 and 27), was oxidized to give aldehyde **37** in good yield (27%, from **(+)-9**) (Scheme 29).



Scheme 29

3.7. Synthesis of aldehyde 38

We also decided to prepare analogues of **1** with a cyclopropane ring instead of the oxirane.[18] The strategy followed started with allylic alcohol **5b** which was obtained from **(+)-9** in 5 steps and with a 36% yield as shown in Scheme 14 and Scheme 15. Subsequently, using the protocol described by Simmons and Smith[19] for asymmetric cyclopropanation, we introduced the cyclopropane ring in the molecule (Scheme 30). The cyclopropanation of **5b** proceeded in 77% yield to yield a 2:1 mixture of diastereomers.



Scheme 30

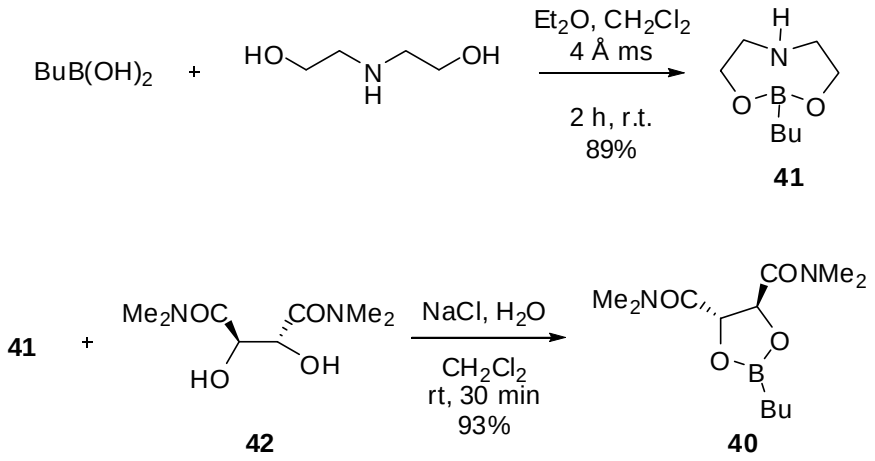
We tried to improve the stereoselectivity of this reaction by using the methodology reported by Charette[20] for asymmetric cyclopropanation of allylic alcohols. One of the most attractive features of this protocol is that high stereoselectivities are usually observed regardless of the substitution pattern of the olefin.

For the synthesis of this dioxaborolane ligand **40**, we followed the procedure described by Charette.[20] This procedure starts with the reaction between butylboronic acid and diethanolamine to give **41** as a white solid in 89% yield. Subsequently, **41** reacts with the amide of tartaric acid **42** to yield the desired dioxaborolane **40** with an overall yield of 83% (Scheme 31)

18 (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589-8627. (b) Taylor, R. E.; Chen, Y.; Galvin, G. M.; Pabba, P. K. *Org. Biomol. Chem.* **2004**, *2*, 2127-2132. (c) Wessjohann, L. A.; Brandt, W. *Chem. Rev.* **2003**, *103*, 1625-1647. (d) Kim, S.-O. *J. Nat. Pod.* **1993**, *56*, 857-863.

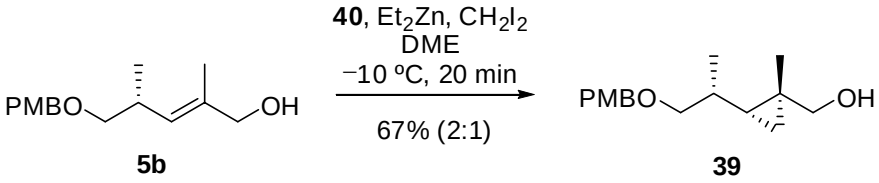
19 (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256-4264. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.*, **1958**, *80*, 5323-5324.

20 Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977-1050.



Scheme 31

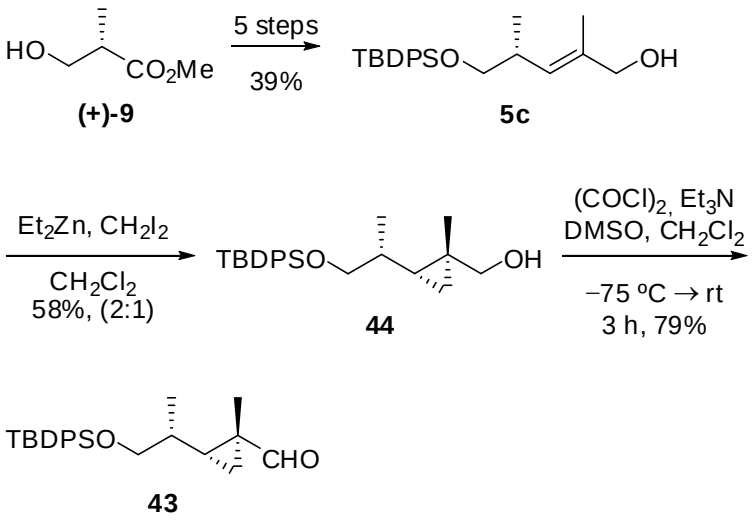
Once **40** had been synthesized it was used in the cyclopropanation of intermediate **5b** to give **39** (Scheme 32). Despite the precedents reported in the literature when employing this strategy, the diastereoselectivity was low and comparable to that obtained before (Scheme 30) and the yield was even lower in this case (67% *vs*. 77%).



Scheme 32

3.8. Synthesis of aldehyde 43

Following the same scheme described for the preparation of **5c** (Scheme 24), the TBDPS protected aldehyde **43** was obtained (Scheme 33). Compound **5c** was obtained in 39% yield in five steps from **(+)-9**. The Simmons-Smith cyclopropanation of the double bond of **44** was performed yielding a 2:1 mixture of diastereomers in favor of the desired one and in 58% yield. Finally, the Swern oxidation of the primary alcohol **44** gave **43** in 17% overall yield (7 steps).

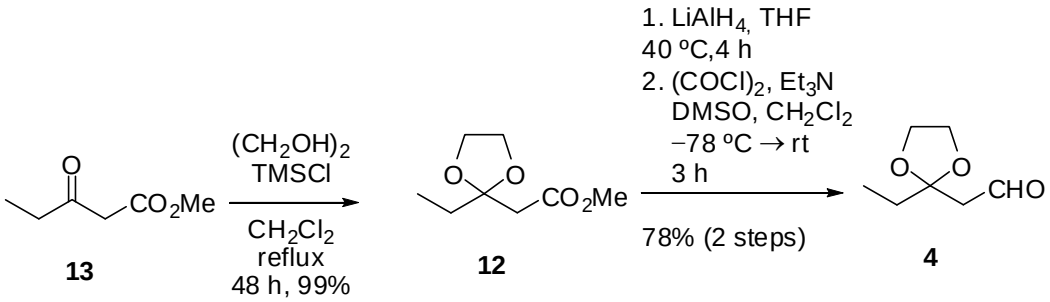


Scheme 33

As in the former case no improvement in the stereoselectivity was achieved using Charette methodology, this method was not tested with the current substrate.

4. Synthesis of the right side aldehyde 4

For the preparation of this synthetic building block **4**, a simple strategy was devised. Starting from the commercially available ketoester **13**, protection of the ketone function was performed by reaction with ethyleneglycol in the presence of trimethylsilyl chloride (TMSCl), to afford acetal **12** quantitatively. Reduction of the ester **12** with $LiAlH_4$ and the subsequent oxidation of the resulting alcohol to the aldehyde using the Swern reaction, furnished aldehyde **4** in 78% yield (2 steps). (Scheme 34).



Scheme 34

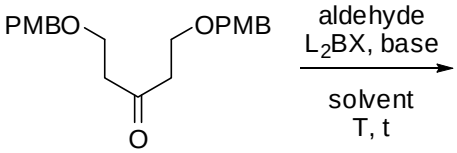
5. Model Aldol reactions

We decided first to study some model reactions of the central ketones **3a** and **3b** with a variety of aldehydes.

5.1. Model aldol reactions using ketone 3a

We started using the lithium enolate of ketone **3a** formed at −78 ºC with an *in situ* generated lithium diisopropyl amide (LDA) in a non protic solvent such as THF. Surprisingly, addition of benzaldehyde to the enolate of **3a** failed to give any aldol product, recovering starting material. Performing the reaction at 0 ºC, no reaction was observed. The same negative result was obtained using isobutyraldehyde instead of benzaldehyde.

We decided to explore two different methods to enolize ketone **3a**. Both protocols take advantage of the π-facial diastereoselectivity in aldol reaction and consist in the use of boranes Bu_2BOTf and Cy_2BCl in the presence of an amine like DIPEA or Et_3N (Scheme 35).



3a

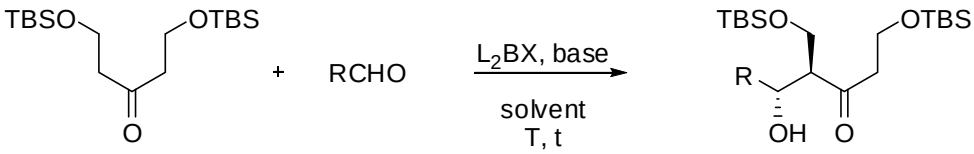
Scheme 35

However, similar negative results were obtained with Bu_2BOTf and diisopropylethylamine as the base in CH_2Cl_2 (−78 ºC or 0 ºC) and benzaldehyde or isobutyraldehyde. Reaction of **3a** with Cy_2BCl and Et_3N in Et_2O also failed to form an enolate of **3a** reactive enough with these aldehydes.

5.2. Model aldol reactions using ketone 3b

We tried the same reaction conditions for ketone **3b** with benzaldehyde and isobutyraldehyde (Table 1). Using Bu_2BOTf we recovered unchanged starting material in all the cases. With Cy_2BCl and benzaldehyde no aldol product was obtained, but in the case of isobutyraldehyde (entry 6, Table 1), aldol **45** was obtained in 56% yield and in a 7:3 diastereomeric ratio (determined by GC/MS). The major aldol was assigned the *anti* configuration based on literature precedent for this type of boron enolates.[21]

*Table 1: Model aldol reaction using ketone **3b**.*



3b **45**: R = Me_2CH

Entry	L_2BX	R	Base	Solvent	T (ºC)	t (h)	Prod (%).
1	Bu_2BOTf	Ph	DIPEA	CH_2Cl_2	–78	1	-
2	Bu_2BOTf	Ph	DIPEA	CH_2Cl_2	0	16	-
3	Bu_2BOTf	Me_2CH	DIPEA	CH_2Cl_2	–78	1	-
4	Cy_2BCl	Ph	Et_3N	Et_2O	–78	1	-
5	Cy_2BCl	Ph	Et_3N	Et_2O	0	16	-
6	Cy_2BCl	Me_2CH	Et_3N	Et_2O	–78	1	**45** (56)

With these results we decided to follow the synthesis of myriaporone **1** using ketone **3b** as the central key moiety.

21 (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287-11314.

The generality of this aldol reaction was studied with several commercially available aldehydes **46-56**. These aldehydes were tested because their similarity with synthetic aldehydes **35-37** (Figure 2).

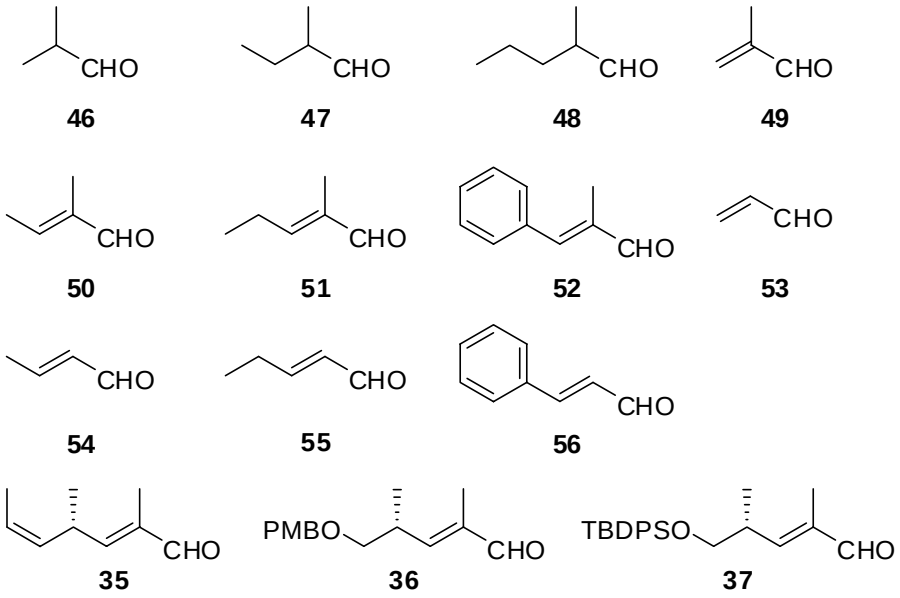
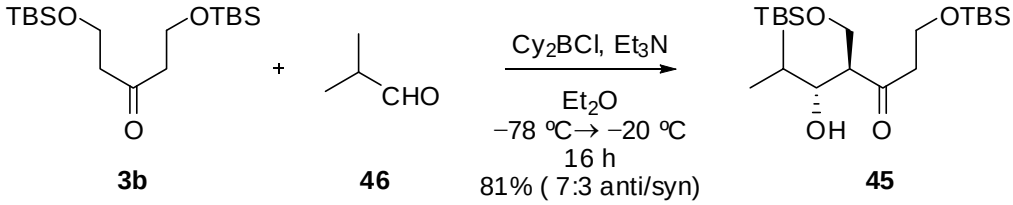


Figure 2

Optimizing the conditions in the aldol reaction between **3b** and **46** (Scheme 39) by changing the temperature and the reaction time we obtained **45** in an 81% yield as a 7:3 mixture of diastereomers (Scheme 36).



Scheme 36

Following the conditions of the reaction detailed in Scheme 40 for each aldehyde (**46-56**) of Figure 2 gave the results summarized in Figure 3. The diastereoselectivity of

each aldol adduct (**45**, **57-66**) was determined by LC-MS and GC-MS. In each case, only the major diastereomer is shown.

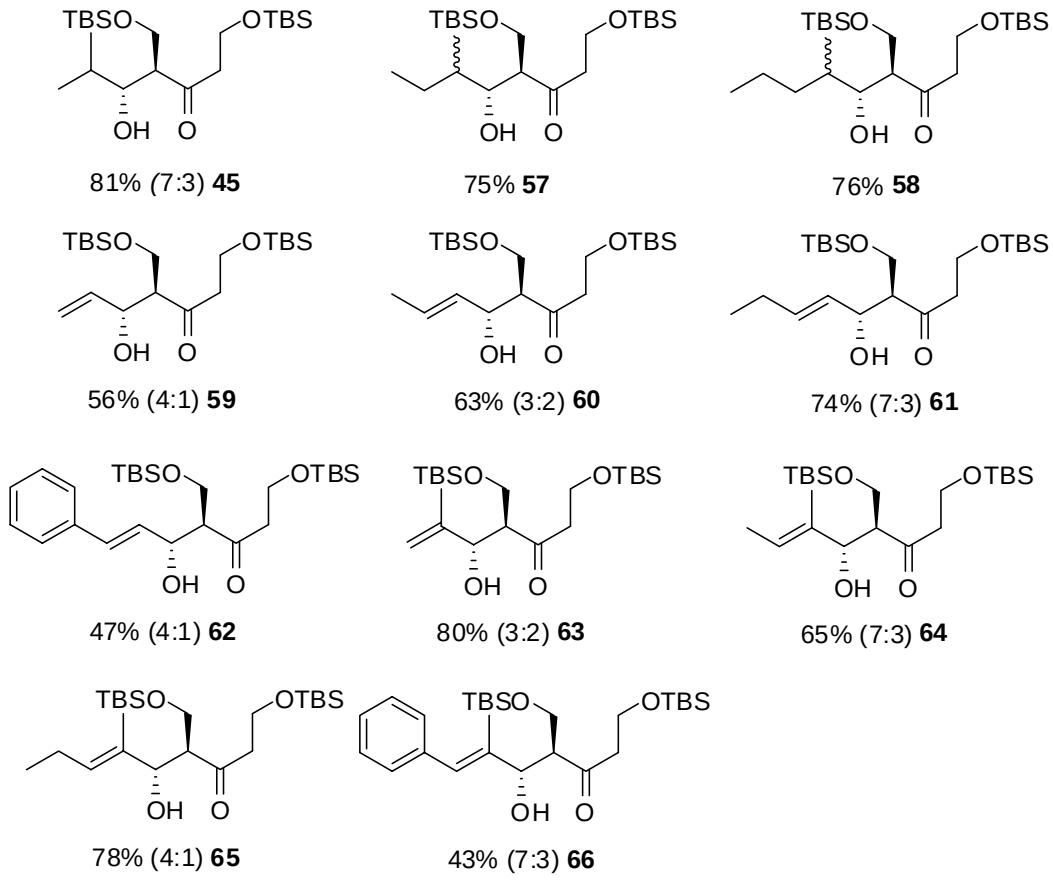


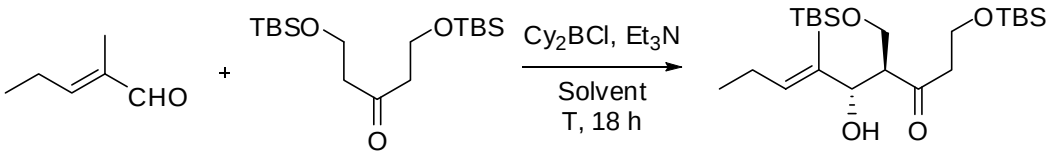
Figure 3

With aldehydes **45-56** good results were obtained and the observed diastereoselectivities were of the same order as those described by Paterson[22] with this kind of substrates. In the case of aldols **57** and **58** the reaction mixture was more complex because of the presence of an additional stereocenter. We did not determine the ratio of four diastereomers in these cases.

We did some optimization experiments using aldehyde **51** in different solvents and temperatures (Table 2).

*Table 2: Aldol reaction between ketone **3b** and aldehyde **51**.*

22 Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585-8588.

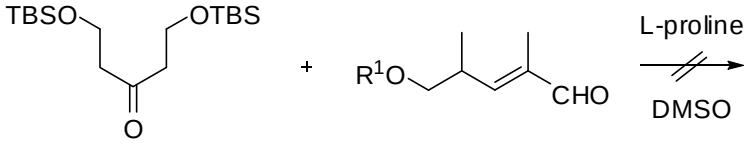


51 **3b** **65**

Entry	Solvent	T (ºC)	Yield (%)	dr (*anti*:*syn*)
1	Et_2O	$-78 \rightarrow -20$	78	4:1
2	Et_2O	-78	20	9:1
3	Et_2O	$-78 \rightarrow 0$	79	1:1
4	pentane	$-78 \rightarrow -20$	21	9:1
5	hexane	$-78 \rightarrow -20$	15	4:1

When the reaction was performed at –78 ºC (Table 2, entry 2) the diastereoselectivity improved (9:1 *anti/syn*), although the yield was low. On the other hand, warming the reaction up to 0 ºC led to a nonstereoselectivity aldol reaction (Table 2, entry 4).

Before continuing with the synthesis of myriaporone **1** we also tried the use of L-proline as catalyst in the reaction between ketone **3b** and aldehydes **36** and **37** using the procedure described by List *et al.*[23] However we only recovered unchanged starting materials under the conditions examined (Scheme 37).



3b

36 (R^1 = PMB)
37 (R^1 = TBDPS)

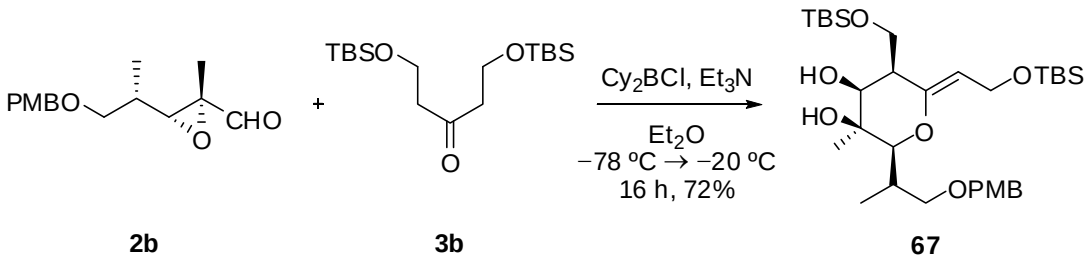
Scheme 37

23 List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

6. First aldol reaction

6.1. First aldol reaction with ketone 3b and aldehydes 2a-c

Loh and Feng[24] reported an anti-aldol reaction for the synthesis of tedanolide already described in the introduction using Paterson's conditions.[25] We performed the reaction between **2b** and **3b** at −20 ºC This reaction afforded tetrahydropyran derivative **67** as a single diastereomer in 78% yield (Scheme 38). It must be noted that in the reaction of the boron enolate of **3b** with aldehydes **2a** and **2c** only unchanged starting materials were recovered.



Scheme 38

The structure of **67** was determined by NMR methods. In Figure 4 are depicted the ^{1}H NOE of the representative cross peaks observed.

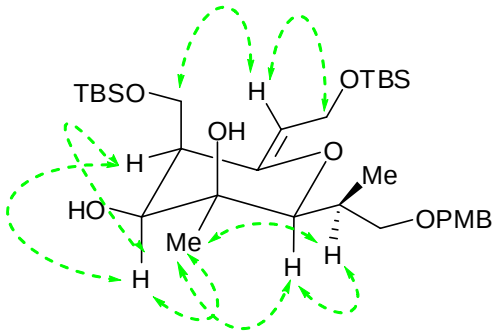
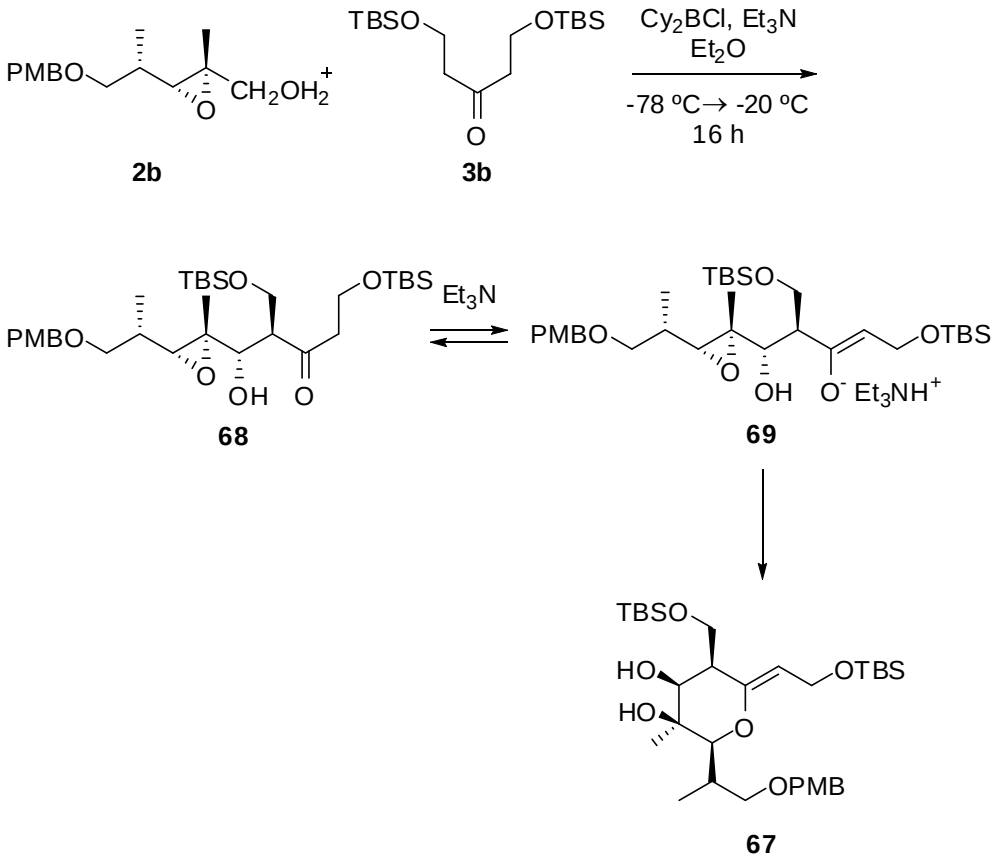


Figure 4

24 Loh, T.-P.; Feng, L.-H. *Tetrahedron Lett.* **2001,** *42,* 3223-3226.
25 Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993,** *58,* 4182-4184.

The result of Scheme 38 shows that in the initial aldol **68** undergoes a 6-*endo-tet* cyclization via the enolate **69** to form cyclic **67**, as it is shown in Scheme 39.



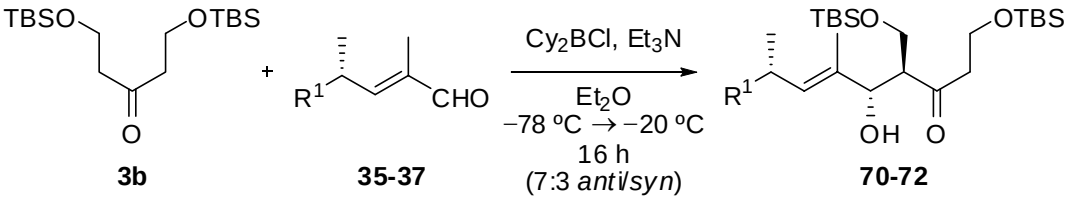
Scheme 39

With this result we decided to change the synthesis introducing the epoxide at the end of the process.

6.2. First aldol reaction with ketone 3b and aldehydes 35-37

Using the conditions described in Scheme 40, we performed the aldol reaction between the three unsaturated aldehydes **35-37** and ketone **3b**. The reactions were performed under the same conditions and the final aldols **70-72** were obtained as 7:3 mixture of diastereomers (Table 3).

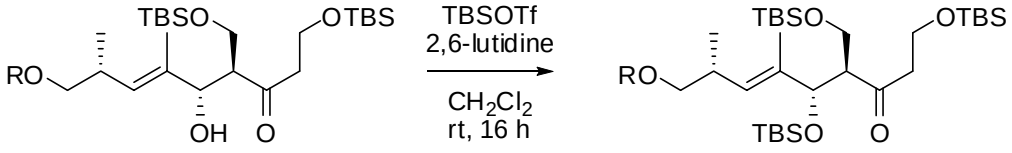
*Table 3: Aldol reaction between ketone **3b** and aldehydes **35-37**.*



Entry	Aldehyde	R^1	Aldol	Yield (%)	dr (anti:syn)
1	**35**	(*Z*) -CH=CHMe	**70**	72	7:3
2	**36**	-CH_2OPMB	**71**	81	7:3
3	**37**	-CH_2TBDPS	**72**	89	7:3

Using aldehyde **35**, aldol **70** was obtained in 72% yield (Table 3, entry 1). Aldols **71** and **72** were obtained in better yields (Table 3, entries 2 and 3) and the syntheses of **36** and **37** were easier to reproduce in consistent yields than that of **35**. Therefore we continued the synthesis of **1** using these two aldehydes instead of **35**.

After performing the left aldol reaction, to continue with the synthesis of myriaporone **1** was necessary to protect the new hydroxyl group generated. For the protection as TBS ether of hydroxyl groups in **71** and **72** we used *t*-butyldimethylsilyl triflate (TBSOTf) and 2,6-lutidine in CH_2Cl_2 at room temperature for 16 h.[26] The protected ethers **73-74** was obtained in excellent yield (Scheme 40).



71 R= PMB
72 R= TBDPS

73 R= PMB, 98%
74 R= TBDPS, 96%

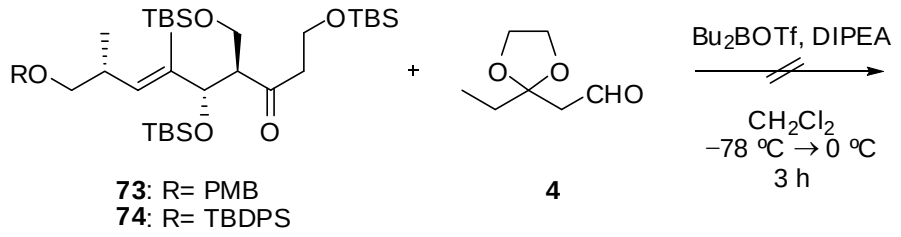
Scheme 40

26 Corey, E. J.; Rücker, H. C.; Hua, D. H. *Tetrahedron Lett*. **1981,** *22*, 3455-3458.

7. Second aldol reaction

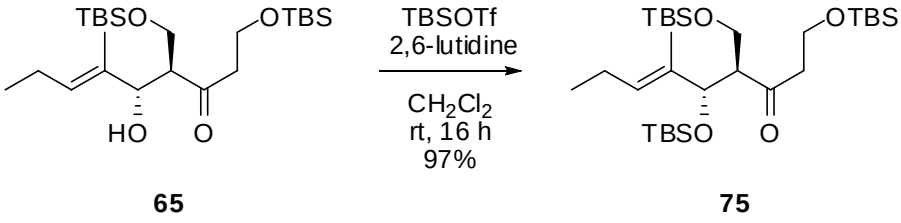
For the next C-C bond formation we needed a *syn* aldol reaction. This relative configuration can be achieved using Bu_2BOTf with DIPEA as base in CH_2Cl_2.[27]

We tried this conditions between the TBS protected the aldols **73** and **74** and the aldehyde **4** (Scheme 41). Unfortunately, the unaltered starting materials were recovered in both cases. After trying the same reaction allowing it to reach room temperature and increasing the reaction time, only traces of aldols were observed.



Scheme 41

To find the experimented conditions for this reaction, we decided to use derivative **75** as model, which was prepared by silylation of aldol **65** (Scheme 42).



Scheme 42

However, as before, ketone **75** failed to give the desired aldol by reaction with aldehyde **4** using Bu_2BOTf and DIPEA.

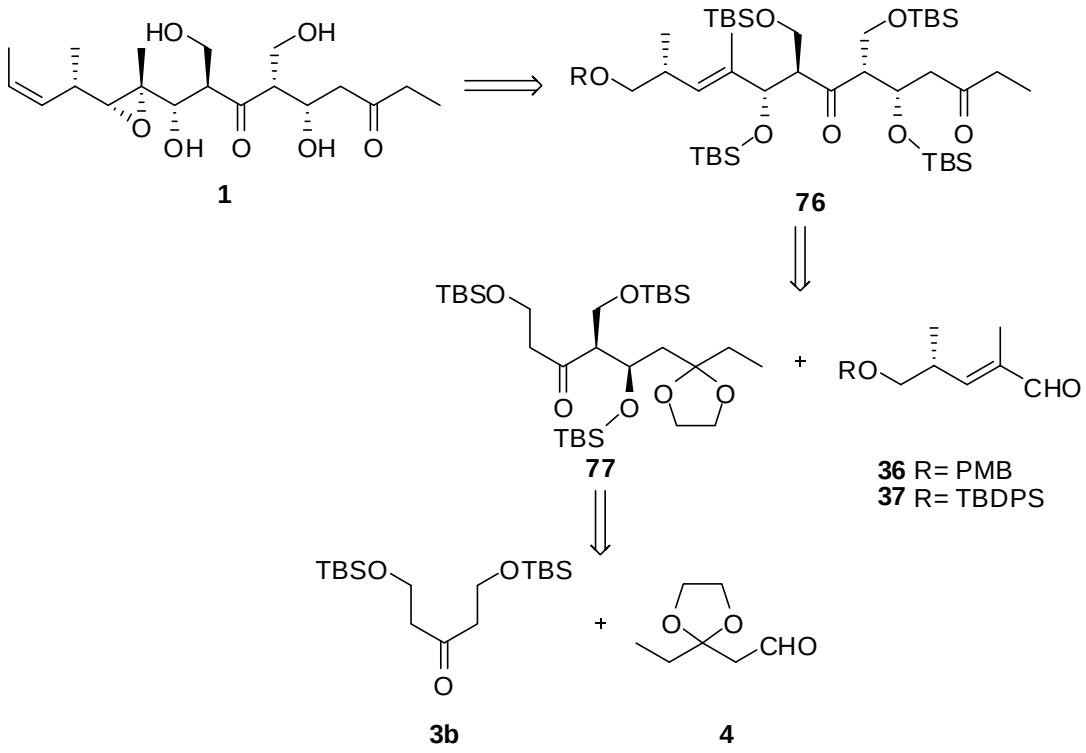
27 Brown, H. C.; Dhar, R. K. Bakshi, R. K. Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441-3442.

The use of $TiCl_4$ and DIPEA has been described as a method for the formation of *syn* aldol products.[28] However, with **73** and **74** we only obtained the starting materials using these conditions. No positive results were obtained at temperatures higher than –78 ºC or using Et_3N as the base.

We decided then to introduce some modifications in the molecule in order to avoid a possible steric hindrance. We tried a different approach. Thus, we tried to change the order aldol reactions introducing the right side aldehyde first. Additionally, we decided to try a lees hindered ketone such as 3-pentanone instead ketone **3b**.

8. From the right side to the left side of the molecule

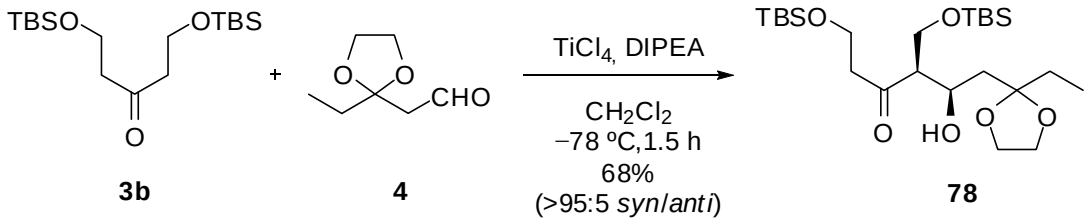
Retrosynthetic plan for the change in the order aldol reactions is summarized in Scheme 43. After an aldol reaction between ketone **3b** and aldehyde **4** and protection of the hydroxyl group, the resulting adduct **77** would react with aldehydes **36**-**37** to give **76** which, after a deprotection and epoxidation yield **1**.



28 Evans, D. A.; Rieger, D. L.; Bilodeau, M T.; Urpi, F. *J. Am. Chem. Soc*. **1991**, *113*, 1047-1049.

Scheme 43

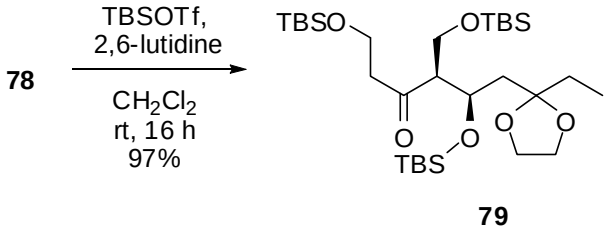
The first aldol reaction was tried with aldehyde **4** and ketone **3b**, with Bu_2BOTf and DIPEA to give the *syn* relative stereochemistry. However, under these conditions, the starting materials were recovered. When the reaction was performed via the Ti (IV) enolate, we obtained the desired aldol unit **78** (Scheme 44) in 68% yield as a >95:5 *syn*:*anti* diastereomeric ratio.



3b **4** **78**

Scheme 44

The generated hydroxyl function of **78** was protected as the TBS ether under the standard conditions giving **79** in 97% yield (Scheme 45).



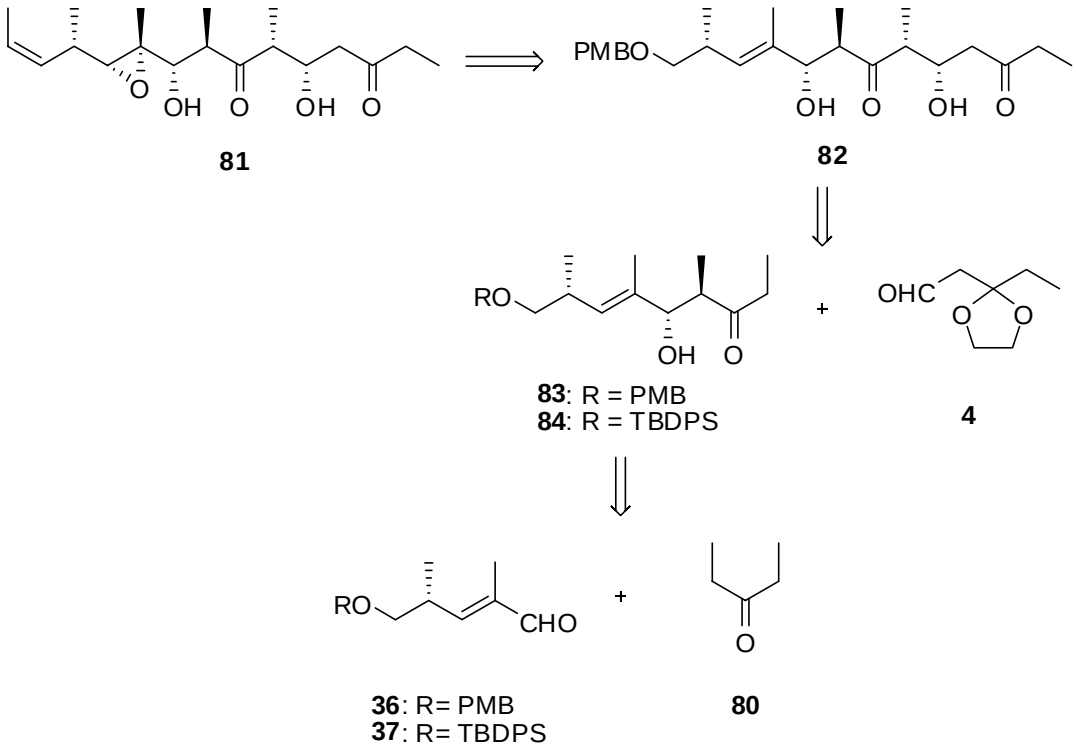
79

Scheme 45

For the next aldol reaction, we tried the reaction between **79** and aldehydes **36** and **37**. However using Cy_2BCl and Et_3N in Et_2O, ketone **79** failed to give the expected product. Similarly negative was the reaction between ketone **79** and aldehyde **51**.

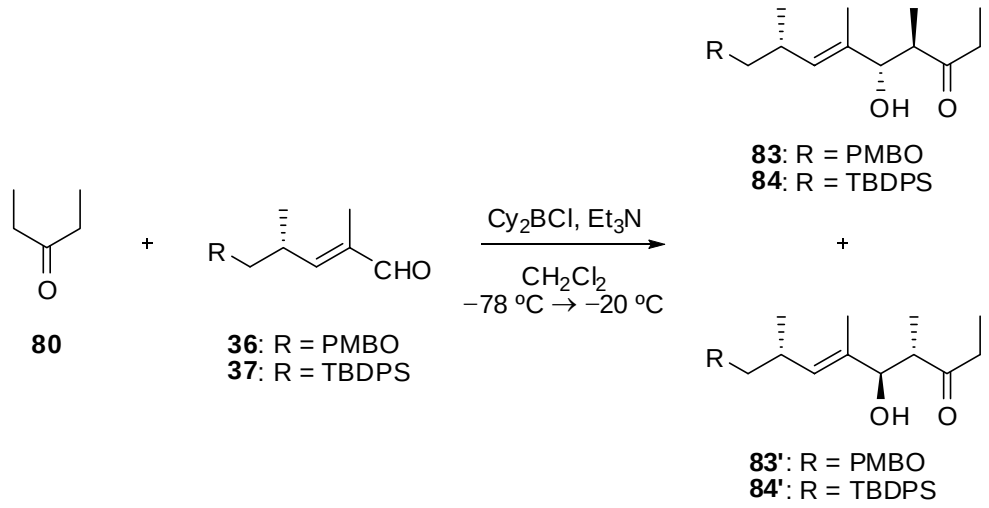
9. Synthesis of bis-deoxymyriaporone. Aldol reaction using 3-pentanone

In Scheme 46 is shown the retrosynthesis for the synthesis of deoxymyriaporone **81** in which the central ketone **3b** has been replaced by 3-pentanone (**80**).



Scheme 46

The results for the first aldol reaction with 3-pentanone **80** were satisfactory. Thus, reaction of **80** with **36** and **37** proceeded in yields very similar to the ones obtained in the aldols reactions with ketone **3b**. In this case, a *ca.* 1:1 mixture of diastereomers **83**/**83'** and **84**/**84'** were obtained (Scheme 47).

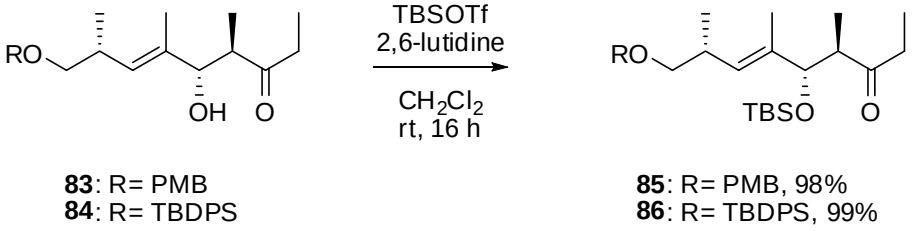


Aldehyde	Products	Yield (%)
36	**83**/**83'**	91
37	**84**/**84'**	98

Scheme 47

We continued the synthesis with the mixture of both diastereomers **83**/**83'** and **84**/**84'**, which could not be separated by chromatography. Here after, we will depict these mixture of diastereomers.

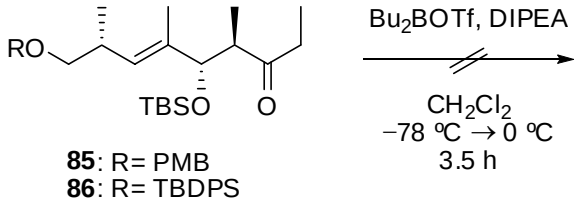
Before the second aldol reaction, the hydroxyl group of the aldols **83** and **84** was protected as usual with TBSOTf and 2,6-lutidine in CH_2Cl_2. The protected aldols **85** and **86** were obtained in excellent yields (Scheme 48).



Scheme 48

For the second aldol reaction we tested the conditions with Bu_2BOTf and diisopropylethylamine in CH_2Cl_2 (Scheme 49). However, with this less hindered ketone

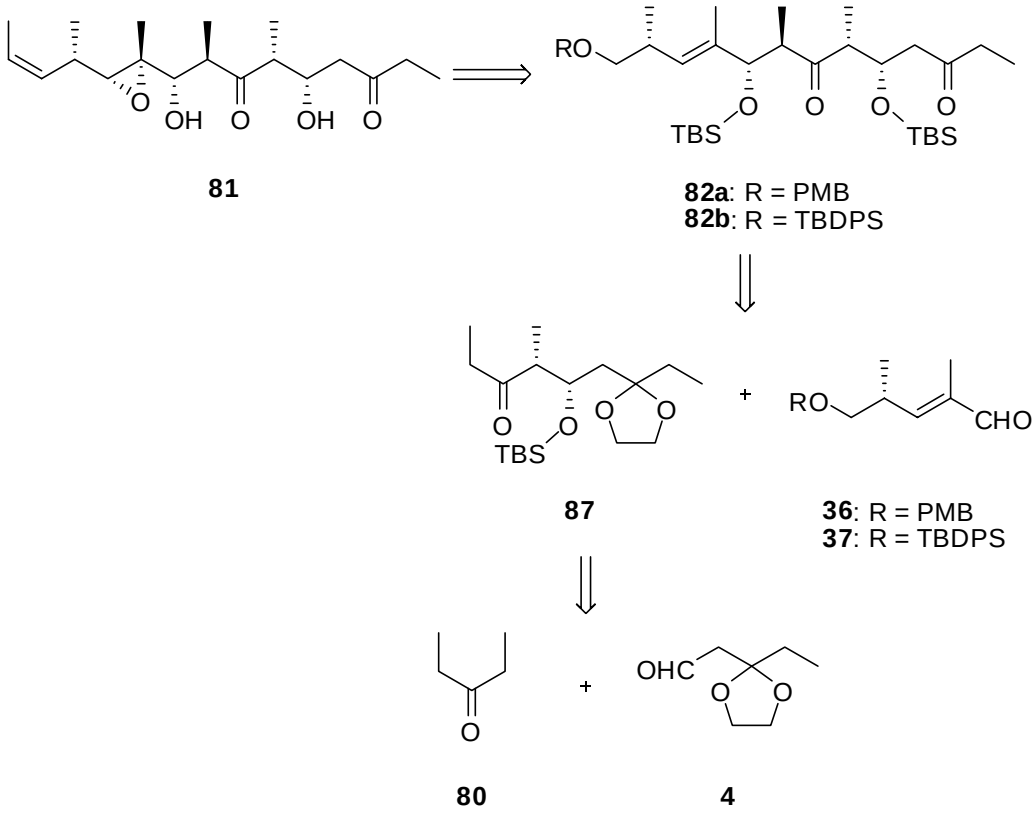
the second aldol also failed. We also tried the reaction with $TiCl_4$ but, again, we just recovered the starting materials.



Scheme 49

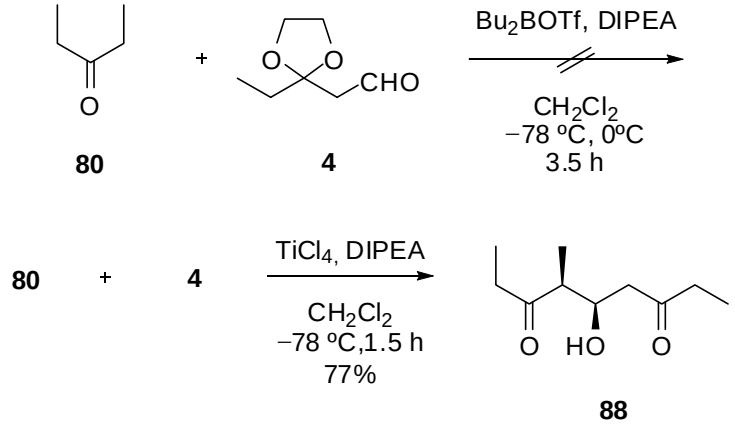
10. From the right side to the left side using 3-pentanone

Finally, we decided to do both changes at the same time, to use 3-pentanone instead of ketone **3b** and change the order to perform the aldol reactions. The details of the retrosynthesis are summarized in Scheme 50.



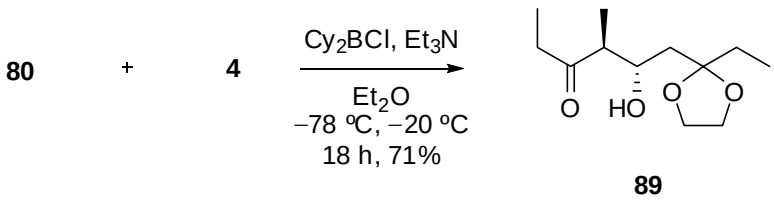
Scheme 50

For the aldol reaction between 3-pentanone **80** and aldehyde **4** we tried first the usual conditions, Bu_2BOTf and DIPEA in CH_2CL_2 at 0 ºC over 3 h. Unfortunately, aldol **87** was not obtained and we recovered the starting materials. On the other hand, after changing reaction time, temperature, concentration, and the base, without satisfactory results, we decided to try the previous tested conditions using $TiCl_4$ (Scheme 51). In this case, the aldol was obtained but the acetal suffered cleavaged during the work up, yielding diketone **88** in 77% yield. With **88** we could not perform a regioselective second aldol reaction with aldehydes **35-37**.



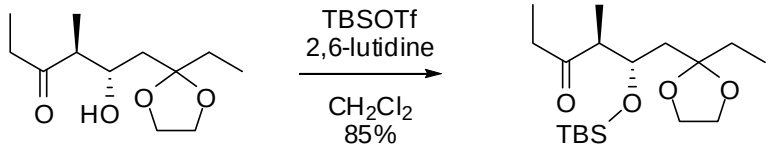
Scheme 51

As expected, reaction between **80** and **4** with Cy_2BCl/Et_3N afforded *anti* aldol **89** (Scheme 52). In this case, the acetal function was not cleavaged. Even though **89** has not the desired relative configuration, we decided to try the next aldol reaction with intermediate **89**.



Scheme 52

Protection of the hydroxyl group of **89** with TBSOTf gave **90** in 85% yield (Scheme 53). All attempts of performing aldol reactions between ketone **90** and aldehydes **36** and **37** using Cy_2BCl/Et_3N failed.

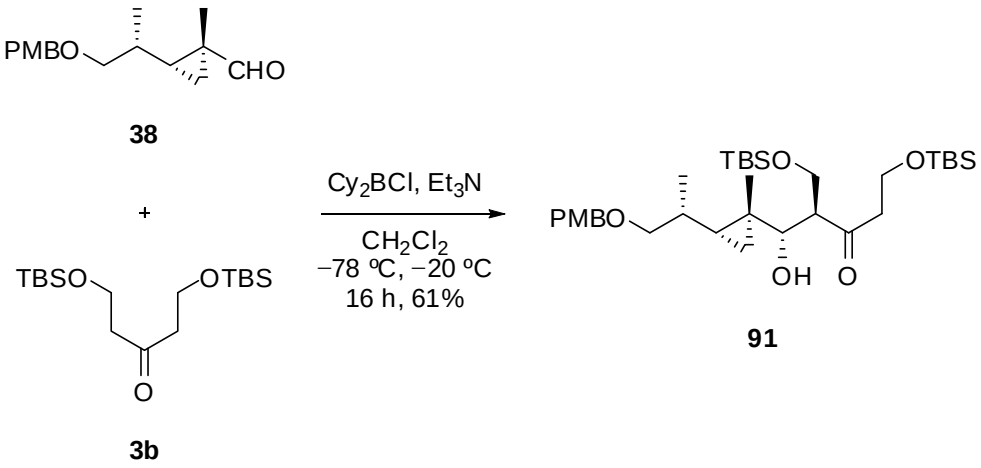


89 **90**

Scheme 53

11. Synthesis of cyclopropyl-myryaporone analogues

For the synthesis of the cyclopropyl analogues, we chose the best conditions found in the assays previously performed with several simple aldehydes. Therefore, reaction of ketone **3b** and aldehyde **38** with Cy_2BCl/Et_3N afforded aldol **91** in 61% yield (Scheme 54). However, the reaction between **3b** and the TBDPS protected aldehyde **43** under the same conditions, gave the unchanged starting materials.

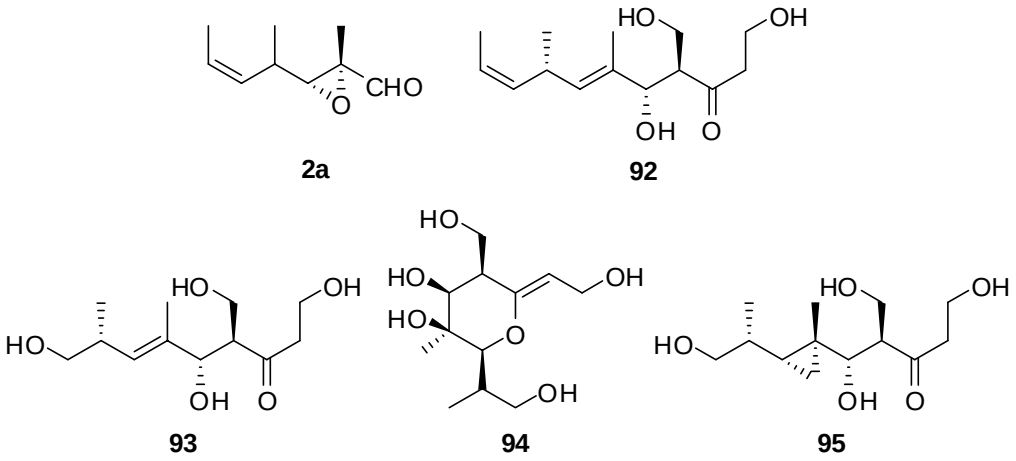


Scheme 54

No reaction was observed between **91** and aldehyde **4** after several attempts under all the condition tested for this reaction.

12. Activity assays

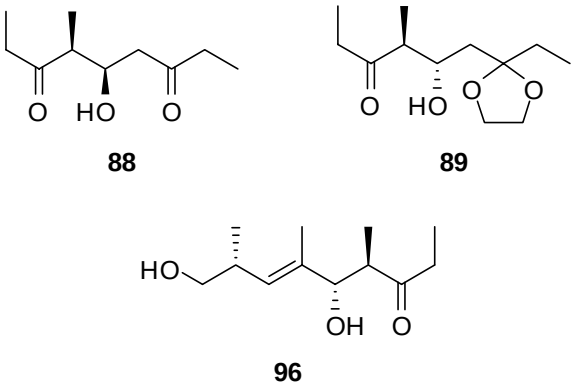
In Figure 5 are shown the intermediates synthesized during this work (**2a**, **92**-**95**) for the synthesis of **1** that were tested for biological activity in PharmaMar.



2a **92** **93** **94** **95**

Figure 5

The activity of some pentanone derivatives intermediates (**88**-**89**, **96**) was also measured (Figure 6). All these compounds were tested in mammalian and colon cancer cells. Noone of these compounds have activity for these therapeutic applications.



88 **89** **96**

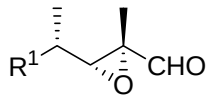
Figure 6

We concluded in agreement with the structure-activity studies done by Taylor[29] and PharmaMar, that the presence of the oxirane ring and the *Z*-double bond is necessary for the biological activity

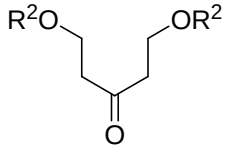
29 Hines, J.; Roy, M.; Cheng, C.; Agapakis, C. M.; Taylor, R. E.; Crews, C. M. *Mol. Biosyst.*, **2006**, *2*, 371-379.

CONCLUSIONS

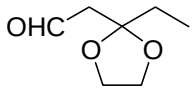
- We have prepared fragments **2a-b**, **3a-b**, **4** and **35-37** for the convergent synthesis of myriaporone 4.



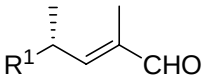
2a: R^1 = -CH=CHMe
2b: R^1 = -CH_2OPMB
2c: R^1 = -CH_2OTBDPS



3a: R^2= PMB
3b: R^2= TBS

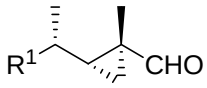


4



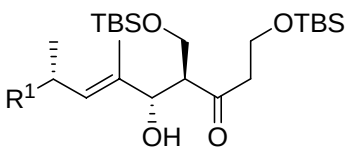
35: R^1 = -CH=CHMe
36: R^1 = -CH_2OPMB
37: R^1 = -CH_2OTBDPS

- We have also prepared cyclopropyl aldehydes **38** and **43** by the cyclopanation of the *α,β*-unsaturated aldehydes using the procedure described by Simmons and Smith. Using the conditions described by Charette we have not obtained better diastereoselectivities.

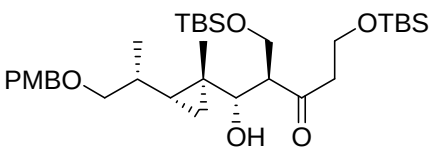


38: R^1 = -CH_2OPMB
43: R^1 = -CH_2OTBDPS

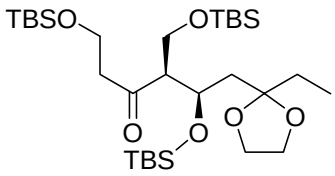
- The aldol reaction of ketone **3b** takes place with different aldehydes using Cy_2BCl and Et_3N to obtain aldols **70-72**, **91** with an *anti* relative configuration and $TiCl_4$ and DIPEA to obtain aldol **79** with a *syn* relative configuration.



70-72

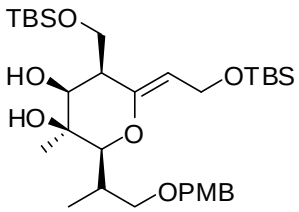


91



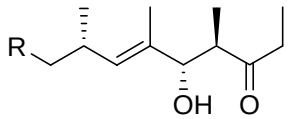
79

- The reaction between aldehyde **2b** and ketone**3b** gave cycle **67**.



- Several attempts to form aldols from **70-72** and **91** with aldehyde **4** failed. Similarly unsuccessful were the attempts to obtained the aldol products from ketone **79** and aldehydes **35-38**.

- Aldol **83** and **84**, analogues of aldols **71-72**, were also prepared using 3-pentanone and aldehydes **36** and **37**.



83: R = PMBO
84: R = TBDPS

- None of the synthesized fragments were active in the biological essays performed at PharmMar.

EXPERIMENTAL SECTION

INDEX

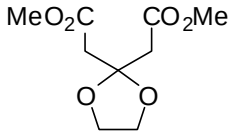
Materials and methods

All reactions were carried out under N_2 or Ar. Solvents were dried using a Solvent Purification System (SPS) or using standard procedures,[1] except for DMF that was purchased from Aldrich anhydrous and packaged under N_2. Analytical thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merk GF_{234}). Flash chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23 ºC on the following spectrometers: Bruker Avance 400 Ultrashield (400 MHz for ^{1}H, and 100 MHz for ^{13}C) and Bruker Avance 500 Ultrashield (500 MHz for ^{1}H, and 125 MHz for ^{13}C) at the *Institut Català d'Investigació Química (ICIQ)*; Bruker AC-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) at the *Departamento de Química Orgánica (UAM)*; Bruker AMX-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) and Bruker AMX-500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) at the *SidI (UAM)*, Varian Unity 300 (300 MHz for ^{1}H, and 75 MHz for ^{13}C) and Varian Unity Inova 500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) at *PharmaMar, S. A. U.* Mass spectra were recorded on a Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers at the *ICIQ* or on a H.P. 5988 A spectrometer at the *Universidad de Santiago de Compostela* or in a NG Auto Spec spectrometer at the *UAM (SidI)* or on a HP 1100 LC/MS at *PharmaMar, S. A. U.* Specific rotation was determined by using a Jasco P-1030 polarimeter (sodium lamp, photomultiplier tube detector with a 589 nm filter and polarimetry cell of 100 mm length) at *PharmaMar, S. A. U.*

1 (a) Burfield, D. R.; Lee, K.-H.; Smithers, R. H. *J. Org. Chem.* **1977**, *42*, 3060-3065. (b) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966-3968. (c) Perrin, D. D.; Armarego, S. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: New York, 1980.

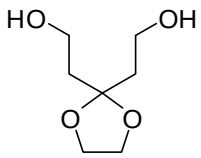
1. Synthesis of the central side ketone

Dimethyl 2,2'-(1,3-Dioxolane-2,2-diyl)diacetate (15)[2]



To a stirred solution of dimethyl 1,3-acetone dicarboxylate (20.0 g, 114.9 mmol) in dry toluene (550 mL) under nitrogen atmosphere were added ethylene glycol (16.0, mL, 287.4 mmol) and *p*-TsOH (2.0 g, 11.49 mmol) The reaction mixture was then heated under reflux for 16 h and quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. Removal of solvent under reduced pressure afforded **15** (22.6 g, 89%) as a colorless oil. R_f = 0.40 (2:1 hexane-EtOAc). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.90 (s, 4H), 3.55 (s, 6H), 2.80 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 65.75 ($2CH_2$), 52.28 ($2CH_3$), 42.50 ($2CH_2$). HRMS-ESI Calcd for $C_9H_{14}O_6Na$ $[M+Na]^+$ 241.0688, Found 241.0697.

2,2'-(1,3-Dioxolane-2,2-diyl)diethanol (10)

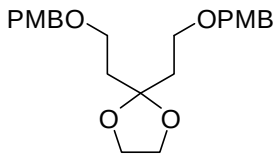


To a stirred suspension of $LiAlH_4$ (6.2 g, 183.5 mmol) in dry THF (300 mL) at 0 ºC was added dropwise a solution of **15** (20.00 g, 91.7 mmol) in dry THF (50 mL) under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and then heated at 40 ºC for 4 h. It was then cooled to 0 ºC, diluted with

2 Yadav, J. S.; Bandyopadhyay, A.; Kunwar, A. C. *Tetrahedron Letters* **2001,** *42(29),* 4907-4911.

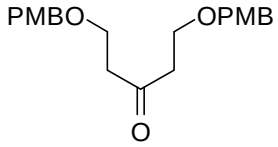
ether and quenched with dropwise addition of saturated aqueous Na_2SO4. Solvent was removed *in vacuo* and the residue was chromatographied (100% EtOAc) to afford **10**[2] as colorless oil (14.28 g, 96%). R_f = 0.45 (100% EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.03 (s, 4H), 3.75 (t, *J* = 5.61 Hz, 4H), 2.65 (bs, 2H), 1.96 (t, *J* = 5.61 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 112.02 (C), 64.71 ($2CH_2$), 58.53 ($2CH_2$), 38.37 ($2CH_2$). HRMS-ESI Calcd for $C_7H_{14}O_4Na$ $[M+Na]^+$ 185.0790, Found 185.0778.

2,2-Bis(2-(4-methoxybenzyloxy)ethyl)-1,3-dioxolane (16)



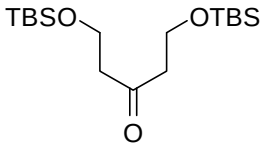
Diol **10** (149.20 mg, 0.92 mmol) was dissolved in 15 mL of dry CH_2Cl_2 and NaH (55 mg, 2.30 mmol) was added at 0 ºC. After 10 min stirring, PMBCl (0.25 mL, 1.84 mmol) was added dropwise. The mixture was stirred at rt during 16 h. Afterwards 25 mL of a saturated solution of NH_4Cl was added and 30 mL of Et_2O. The phases were separated and the aqueous layer was extracted with 2 x 20 mL of Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was chromatography (10:1 hexane-EtOAc) to give **16** (292 mg, 79%) as a colorless oil. R_f = 0.37 (10:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, *J* = 8.57 Hz, 2H), 6.88 (d, *J* = 8.57 Hz, 4H), 4.42 (s, 4H), 3.97 (s, 4H), 3.81 (s, 6H), 3.55 (t, *J* = 6.47 Hz, 4H), 2.98 (t, *J* = 6.47 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.77 (C), 134.19 (2C), 129.94 ($4CH_2$), 114.41 ($4CH_2$), 110.19 (2C), 73.37 ($2CH_2$), 66.53 ($2CH_2$), 65.43 ($2CH_2$), 55.92 ($2CH_3$), 38.06 ($2CH_2$). HRMS-ESI Calcd for $C_{23}H_{30}NaO_6$ $[M+Na]^+$ 425.4669, Found 425.4678.

1,5-Bis(4-methoxybenzyloxy)pentan-3-one (3a)



Acetal **16** (299.5 mg, 0.74 mmol) was dissolved in 20 mL of THF, 10 mL of a HCl (5%) aqueous solution were added and the reaction was stirred for 1 h under reflux. Afterwards, 20 mL of water were added and the phases were separated. The aqueous layer was extracted with 2 x 10 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography in 4:1 hexane-EtOAc to give **3a** (266.7 mg, 96%) as a yellow oil. R_f = 0.36 (4:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, J = 8.76 Hz, 4H), 6.87 (d, J = 8.76 Hz, 4H), 4.44 (s, 4H), 3.80 (s, 6H), 3.71 (t, J = 5.15, 4H), 2.70 (t, J = 5.15, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.8 (C), 159.8 (2C), 129.8 (2C), 128.5 (4CH), 114.2 (4CH), 74.7 ($2CH_2$), 65.0 ($2CH_2$), 45.1 ($2CH_2$). HRMS-ESI Calcd for $C_{21}H_{26}NaO_5$ $[M+Na]^+$ 381.1678, Found 381.1683.

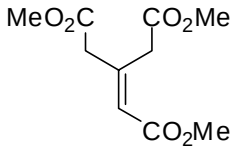
1,5-Bis-(*tert*-butyldimethylsilanyloxy)methylpentan-3-one (3b)



Amberlyst-15 (0.80 g) was added to a stirred solution of diol **10** (11.90 g, 73.40 mmol) in 150 mL of a mixture of CH_2Cl_2/MeOH (2:1). After 16 h at room temperature 200 mL of a saturated aqueous solution of $NaHCO_3$ were added. The organic phase was separated and the aqueous layer was extracted with 2 x 50 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was dissolved in 100 mL of dry CH_2Cl_2 and at 0 ºC imidazol (50.00 g, 734.00 mmol) was added and the solution was stirred during 15 min, afterwards TBSCl (55.30 g, 367 mmol) was added and stirred at room temperature during 1 hour. A saturated aqueous solution of NH_4Cl was added, the organic phase was separated and

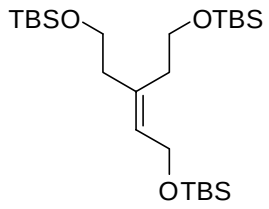
the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (10:1 hexane-EtOAc) to give **3b** (17.43 g, 58% yield) as a colorless oil. R_f = 0.46 (10:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.88 (t, J = 6.47 Hz, 4H), 2.65 (t, J = 6.47 Hz, 4H), 0.87 (s, 18H), 0.05 (s, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.78 (C), 58.80 ($2CH_2$), 46.69 ($2CH_2$), 26.03 ($6CH_3$), 18.38 (2C), -5.16 ($4CH_3$). HRMS-ESI Calcd for $C_{17}H_{38}O_3Si_2Na$ $[M+Na]^+$ 369.2257, Found 369.2245.

Dimethyl 3-(2-Methoxy-2-oxoethyl)pent-2-enedioate (19)



To a stirred solution of ketone **11** (1.00 g, 62.32 mmol) in 15 mL of toluene, Ph_3PCHCO_2Me (2.90 g, 9.12 mmol) was added. The reaction was refluxed during 18 h to yield compound **19** (0.99 g, 72%) as a yellow solid which was filtered and purified by column chromatography R_f = 0.3 (4:1 Hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.96 (s, 1H), 3.87 (s, 2H), 3.70 (s, 3H) 3.69 (s, 6H), 3.30 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4 (C), 170.0 (C), 165.9 (C), 146.0 (C), 122.3 (CH), 52.2 (CH_3), 52.0 (CH_3), 51.3 (CH_3), 43.6 (CH_2), 36.5 (CH_2). HRMS-ESI Calcd for $C_{10}H_{14}NaO_6$ $[M+Na]^+$ 253.0688, Found 253.0685.

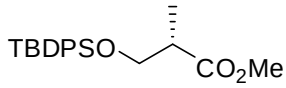
1,5-Bis[(*tert*-butyldimethylsilyl)oxy]-3-[2-(*tert*-butyldimethylsilyloxy)ethyl]-pente-2-ene (21)



At 0 ºC and under N_2, a suspension of triester **19** (2.47 g, 10.73 mmol) in 50 mL of dry THF, $LiAlH_4$ (1.22 g, 32.19 mmol) was added slowly. The reaction was heated at 40 ºC during 4 h. After the addition of 10 g $Na_2SO_4.10H_2O$, the crude was filtered and the residue concentrated in vacuo to yield trialcohol **20** in good yield (1.29 g, 82%), which was used directly in the next step of the synthesis. Trialcohol **20** (1.16 g, 7.83 mmol) was redissolved in 50 mL of CH_2Cl_2 and imidazol (1.87 g, 27.44 mmol) and TBSCl (3.59 g, 23.81 mmol) were added at 30 ºC. The mixture was stirred overnight at the same temperature. 100 mL of water were added and the phases were separated. The aqueous phase was extracted with 3 x 50 mL of CH_2Cl_2, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*, the residue was purified by column chromatography R_f = 0.4 (8:1 Hexane:EtOAc) to yield trisilylether **21** (7.12 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.43 (m, 1H), 4.20(d, J = 6.2 Hz, 2H), 4.15 (t, J = 6.9 Hz, 3H), 3.61 (t, J = 6.9 Hz, 3H), 2.36 (m, 2H), 2.24 (m, 2H) 0.90 (s, 9H), 0.88 (s, 18H), 0.06 (s, 6H), 0.04 (s, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8 (C), 122.4 (CH), 61.2 ($2CH_2$), 59.4 (CH_2), 42,5 (CH_2), 36.3 (CH_2), 26.0 ($6CH_3$), 24.7 ($4CH_3$), 18.3 (2C), 17.8 (C), -5.2 ($4CH_3$), -5.0 ($2CH_3$). HRMS-ESI Calcd for $C_{25}H_{56}O_3Si_3Na$ $[M+Na]^+$ 511.3435, Found 511.3437

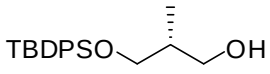
2. Synthesis of the left aldehyde with TBDPS as protecting group

Methyl (*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropanoate (8c)



To a stirred solution of ethyl (*S*)-(+)-3-hydroxy-2-methylpropionate (2.99 mL, 27.09 mmol) in 15 mL of dry CH_2Cl_2, imidazol (2.77 g, 40.63 mmol) and TBDPSCl (2.76 g, 40.63 mmol) was added dropwise at 0 ºC. After the addition the reaction was stirred during 16 h at room temperature. R_f = 0.47 (4:1 hexane-EtOAc). The reaction crude was washed with 50 mL of a NH_4Cl saturated aqueous solution, phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **8c** (9.60 g, 98%) as a colorless oil which could be used in the next step without further purifications. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, *J* = 6.5 Hz, 4H), 7.43-7.35 (m, 6H), 3.82 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.72 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.68 (s, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.30 (C), 135.52 (4CH), 133.45 (2C), 129.58 (2CH), 127.59 (4CH), 65.87 (CH_2), 51.47 (C), 42.35 (CH_3), 26.66 ($3CH_3$), 19.18 (CH), 13.41 (CH_3). HRMS-ESI Calcd for $C_{21}H_{28}O_3SiNa$ $[M+Na]^+$ 379.1705, Found 379.1688. $[\alpha]_D^{25}$ = –16.5 (c 1.1, $CHCl_3$).

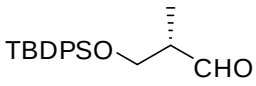
(*R*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropan-1-ol (33)



At 0 ºC and under N_2 atmosphere, a solution 1.0 M in hexane of DIBAL-H (187.31 mL, 187.31 mmol) was added to a solution of ester **8c** (31.77 g, 89.19 mmol) in 140 mL of dry CH_2Cl_2. The reaction was stirred at 0 ºC during 3 h. 100 mL of Na^+/K^+ tartrate saturated solution and 100 mL of EtOAc were added and the mixture

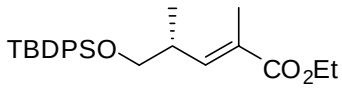
stirred until the phases were separated. The aqueous layer was extracted with 3 x 50 mL of EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **33** (20.51 g, 71%) as a colorless oil. The product was used in the next step without further purifications. R_f = 0.34 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 6.6 Hz, 4H), 7.44-7.36 (m, 6H), 3.88 (dd, J = 10.1, 4.5 Hz, 1H), 3.62 (m, 2H), 3.37 (dd, J = 10.1, 7.7 Hz, 1H), 1.83 (m, 1H), 0.98 (s, 9H), 0.96 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.02 (2C), 132.61 (4CH), 130.11 (2C), 128.43 (4CH), 66.52 (CH_2), 66.41 (CH_2), 38.87 (CH), 25.63 ($3CH_3$), 19.22 (C), 13.02 (CH_3). HRMS-ESI Calcd for $C_{20}H_{29}O_2Si$ $(M+H)^+$ 329.1931, Found 329.1933. $[\alpha]_D^{25}$= –18.9 (c 1.3, $CHCl_3$).

(S)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropanal (7c)



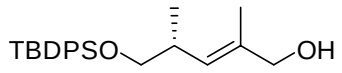
At –78 ºC and under N_2 atmosphere, $(COCl)_2$ (5.41 mL, 62.05 mmol) was dissolved in 50 mL of dry CH_2Cl_2 and DMSO (8.80 mL, 124.10 mmol) was added dropwise, after 30 min, a solution of alcohol **33** (12.74 g, 38.78 mmol) was added and the mixture was stirred during 1 h. Then Et_3N (35.13 mL, 252.07 mmol) was added and the reaction was allowed to reach room temperature and was completed after 2 h. The reaction was quenched by addition of 100 mL of saturated aqueous $NaHCO_3$, the phases were separated and the aqueous phase was extracted twice with 2x50 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to yield aldehyde **7c** (9.75 g, 77%) which is used in the next reaction without further purifications. R_f = 0.43 (8:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 7.65 (d, J = 6.41 Hz, 4H), 7.42-7.34 (m, 6H), 3.92 (m, 2H), 2.55 (m, 1H), 1.12 (d, J = 7.1 Hz, 3H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.11 (C), 134.17 (2C), 132.65 (4CH), 130.13 (2C), 128.40 (4CH), 62.74 (CH_2), 49.49 (CH), 25.62 ($3CH_3$), 19.28 (C), 10.05 (CH_3). HRMS-ESI Calcd for $C_{20}H_{26}O_2SiK$ $(M+K)^+$ 365.6025, Found 365.6016. $[\alpha]_D^{25}$= –17.1 (c 1.2 $CHCl_3$).

(*R,E*)-Ethyl 5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-enoate (6c)



To a stirred solution of aldehyde **7c** (12.66 g, 38.78 mmol) in 50 mL of CH_2Cl_2, (ethoxycarbonyl)ethylidene triphenylphosphorane[3] (25.29g, 69.79 mmol) was added and the reaction was stirred over 16 h at room temperature. 100 mL of water was added and the phases were separated, the aqueous layer was extracted twice with 50 mL CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purificated by silica gel flash chromatography (9:1 hexane:EtOAc) to yield compound **6c** (11.98 g, 76%) as pale yellow oil. R_f = 0.47 (8:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67-7.62 (m, 4H), 7.44-7.34 (m, 6H), 5.78 (dd, *J* = 9.6, 1.3 Hz, 1H), 3.68 (s, 3H), 3.54 (d, *J* = 5.9 Hz, 2H), 3.44-3.33 (m, 1H), 1.89 (d, *J* = 1.3 Hz, 3H), 1.04 (s, 9H), 1.02 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3 (C), 144.4 (2C), 135.7 (2CH), 135.6 (2CH), 134.0 (C), 129.6 (2CH), 129.6 (2CH), 129.4 (CH), 127.8 (CH), 127.6 (CH), 67.7 (CH_2), 60.3 (CH_2), 36.2 (C), 26.8 ($3CH_3$), 19.3 (C), 16.3 (CH_3); 14.3 (CH_3), 12.6 (CH_3). HRMS-ESI Calcd for $C_{27}H_{39}O_3Si$ $(M+C_2H_5)^+$ 439.2669, Found. 439.2668. $[\alpha]_D^{25}$ = -41.9 (c 1.2, $CHCl_3$).

(*R,E*)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-en-1-ol (5c)

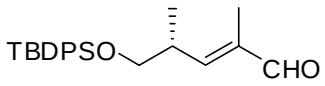


To a stirred solution of ester **6c** (6.20g, 15.10 mmol) in 20 mL of CH_2Cl_2, a 1.0 M solution in hexanes of DIBAL-H (31.71 mL, 31.71 mmol) was added at 0 ºC, after 3 h. the reaction was completed. 50 mL of saturated aqueous solution of Na^+/K^+ tartrate and 50 mL of EtOAc was added and stirred until separation of phases. The aqueous

3 Bestmann, H. J.; Haeberlein, H.; Eisele, W. *Chem Ber*. **1966**, *99*, 1198-1207.

phase was extracted with 2x50 mL of EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was eliminated under reduced pressure. The product was chromatography (4:1 hexane:EtOAc) and **5c** was obtained as a colorless oil (5.57 g, 96%). R_f = 0.22 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.63 (m. 4H), 7.46-7.35 (m. 6H), 5.16 (dq, *J* = 11.9, 6.9 Hz, 1H), 3.95 (s, 2H), 3.51 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.47 (dd, *J* = 9.6, 8.2 Hz, 1H), 2.63 (m, 1H), 1.92 (bs, 1H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.04 (s, 9H), 1.00 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.4 (2C), 135.7 (2CH), 135.6 (2CH), 134.0 (C), 129.6 (2CH), 129.6 (2CH), 129.4 (CH), 127.8 (CH), 127.6 (CH), 68.9 (CH_2), 68.5 (CH_2), 35.0 (C), 26.8 ($3CH_3$), 19.3 (C), 17.2 (CH_3); 13.9 (CH_3). HRMS-ESI Calcd for $C_{23}H_{32}NaO_2Si$ $[M-H]^+$ 391.2069, Found 391.2052. $[\alpha]_D^{25}$ = –14.8 (c 1.0 $CHCl_3$).

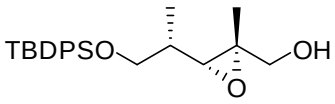
(*R*,*E*)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-enal (37)



At –78 ºC and under N_2 atmosphere, $(COCl)_2$ (80 μL, 0.87 mmol) was dissolved in dry 10 mL CH_2Cl_2, then DMSO (0.12, 1.74 mmol) was added and stirred during 30 min, after a solution of alcohol **5c** (0.20 g, 054 mmol) was added dropwise, and the mixture was stirred at –78 ºC during 1 h. Then Et_3N (0.49 mL, 3.52 mmol) was added dropwise, the reaction was allowed to reach room temperature and, after 3 h, the reaction was quenched with 10 mL of saturated aqueous solution of $NaHCO_3$, the phases were separated and the aqueous one was extracted with 3 x 10 mL CH_2Cl_2. The product was purified by flash chromatography (4:1 hexane:EtOAc) to yield aldehyde **37** (0.13 g, 68%) as a colorless oil. R_f = 0.57 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (s, 1H), 7.63 (d, *J* = 6.82 Hz, 4H),), 7.44-7.34 (m, 6H), 6.21 (dd, *J* = 9.6, 1.3 Hz, 1H), 3.66 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.60 (dd, *J* = 9.6, 8.2 Hz, 1H), 2.93 (m, 1H) 1.72 (d, *J* = 1.3 Hz, 3H), 1.06 (d, *J* = 6.2 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.95 (CH), 154.42 (CH), 135.93 (C), 134.02 (2C), 132.61 (4CH) 130.12 (2CH), 128.44 (4CH), 70.52 (CH_2), 37.87 (CH), 25.60 ($3CH_3$), 19.23 (C), 17.88 (CH_3),

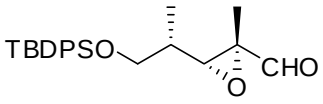
9.21 (CH_3). HRMS-ESI Calcd for $C_{23}H_{30}O_2SiNa$ $[M+Na]^+$ 389.1913, Found 389.1808. $[\alpha]_D^{25}$ = –45.2 (c 1.1, $CHCl_3$).

(2*S*,3*R*,4*S*)- 5-(*tert*-butyldiphenylsilyoxy)-2,4-dimethyl-2-oxiranyl-1-pentanol (34)



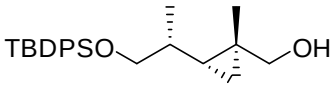
At –78 ºC a solution of TBHP (0.27 mL, 1.47 mmol) and $Ti(O\text{-}iPr)_4$ (0.24 mL, 0.81 mmol) in 25 mL of CH_2Cl_2 were stirred and a solution of allylic alcohol **5c** (0.30 g, 0.81 mmol) in 10 mL of CH_2Cl_2 was added. After 20 min (-)-DET (0.14 mL, 0.81 mmol) was slowly added and the reaction was warmed until 0 ºC in 1.5 h. 10 mL of a solution of tartaric acid (10%) was added and was stirred during 30 min at 0 ºC and during 30 min at r.t. The phases were separated. The organic phase was concentrated and was solved again in 20 mL Et_2O, and 20 mL of a solution of NaOH 1 N was added at 0 ºC, and was stirred during 30 min left. The organic phase was separated, dried and concentrated. The product was chromatographied (6:1 hexane:EtOAc) and epoxialcohol **34** was obtained as a colorless oil (0.21 g, 68% 10:1). R_f = 0.54 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (m, 4H), 7.44-7.37 (m, 6H), 3.66 (dd, *J* = 12.2, 4.5 Hz, 1H), 3.62 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.56 (dd, *J* = 8.5, 4.9 Hz, 1H), 3.54 (dd, *J* = 7.4, 1.7 Hz, 1H), 2.88 (d, *J* = 9.4 Hz, 1H), 1.79 (m, 1H), 1.27 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.03 (2C), 130.11 (6CH), 129.52 (4CH), 71.92 (CH), 67.24 (CH_2), 66.67 (CH_2), 59.01 (C), 33.37 (CH), 26.82 ($3CH_3$), 20.98 (CH_3), 19.24 (C), 14.60 (CH_3). HRMS-ESI Calcd for $C_{23}H_{32}O_3SiNa$ $[M+Na]^+$ 407.2018, Found 407.2017. $[\alpha]_D^{25}$ = +21.4 (c 1.0, $CHCl_3$).

(2*S*,3*R*)-3-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl]-2-methyloxirane-2-carbaldehyde (2c)



Following the same procedure to synthesize aldehyde **37,** compound **2c** was obtained using the following amounts of reagents: epoxyalcohol **34** (0.15 g, 0.38 mmol), $(COCl)_2$ (53 μL, 0.61 mmol), DMSO (86 μL, 22 mmol) and Et_3N (0.34 mL, 2.47 mmol), in 5 mL of CH_2Cl_2. The mixture was stirred for 2 h at room temperature, after the work-up the crude of the reaction was purified by flash chromatography (6:1 hexane-EtOAc) to obtain aldehyde **2c** as pale yellow oil (103 mg, 69%, dr = 10:1). R_f = 0.62 (4:1 EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (s, 1H), 7.61-7.57 (m, 4H), 7.45-7.35 (m, 6H), 3.64 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.52 (dd, *J* = Hz, 1H), 2.99 (d, *J* = 9.1 Hz, 1H), 1.95 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.8 (CH), 134.1 (2C), 130.2 (6CH), 129.5 (4CH), 72.1 (CH), 66.1 (CH_2), 59.0 (C), 33.2 (CH), 26.7 ($3CH_3$), 21.0 (CH_3), 19.2 (C), 14.6 (CH_3). HRMS-ESI Calcd for C_{24} H_{34} O_4 Na Si $(M+NaOCH_4)^+$ 437.2124, Found 437.2123. $[\alpha]_D^{25}$ = +61.4 (c 1.7, $CHCl_3$).

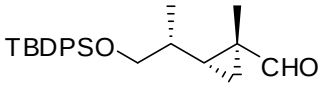
(2*R*,3*R*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethyl-2-cyclopropyl-1-pentanol (44)



At -60 ºC and under N_2, in 2 mL of dry CH_2Cl_2, a 1.0 M solution of $ZnEt_2$ in hexanes (1.92 mL, 1.92 mmol) and CH_2I_2, (0.15 mL, 1.92 mmol) were stirred until formation of a white precipitate. Then the solution was warmed until 0 ºC for 5 min and cooled until -65 ºC. The allylic alcohol **5c** (0.71 g, 1.92 mmol) was added in 2 mL of dry CH_2Cl_2 and the reaction was warmed until r.t. and stirred during 15 more min The reaction was treated with 4 mL of saturated solution NH_4Cl (pH 8) and the organic phase was separated; the aqueous phase extracted with Et_2O and the combine organic phases were dried over $MgSO_4$, filtered and concentrated. The crude of the reaction was chromatographied (6:1 hexane-EtOAc), to yield the hydroxycyclopropane **44** as a colorless oil (0.43 g, 58%, dr = 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (m, 4H), 7.40 (m, 6H), 4.63 (s, OH), 3.68(dd, J= 9.7, 4.4 Hz, 1H), 3.60 (dd, J= 9.8, 4.4 Hz, 1H), 3.48

(d, *J* = 4.6 Hz, 1H), 3.25 (d, J= 5.4 Hz, 1H), 1.85 (m, 1H), 1.06 (d, J= 3.0 Hz, 3H), 1.05 (s, 9H), 1.02 (s, 3H), 0.53 (m, 1H), 0.48 (m, 1H), 0.18 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.0 (2C), 130.2 (6CH), 129.5 (4CH), 70.8 (CH_2), 67.3 (CH_2), 44.5 (CH), 26.7 ($3CH_3$), 22.0 (CH_3), 19.2 (C), 18.5 (C), 17.3 (CH_2), 16.9 (CH), 14.5 (CH_3). HRMS-ESI Calcd for $C_{24}H_{34}O_2NaSi$ $(M+NaOCH_4)^+$ 405.2226, Found 405.2226. $[\alpha]_D^{25}$ = +23.1 (c 1.0, $CHCl_3$).

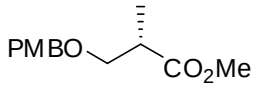
(1*S*,2*R*)-2-[(*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl]-1-methylcyclopropane carbaldehyde (43)



Following the same procedure to synthesize aldehyde **37,** compound **43** was obtained using the following amounts of reagents: hydroxycyclopropane **44** (0.20 g, 0.52 mmol), $(COCl)_2$ (73 μL, 0.87 mmol), DMSO (0.12 mL, 1.67 mmol) and Et_3N (0.47 mL, 3.40 mmol), in 5 mL of CH_2Cl_2. The mixture was stirred for 2 h at room temperature, after the work-up the crude of the reaction was purified by flash chromatography (4:1 hexane-EtOAc) to give **43** as a colorless oil (0.15 g, 75%, dr = 2:1). R_f = 0.42 (4:1 EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (2, 1H), 7.66 (m, 2H), 7.62 (m, 2H), 7.38 (m, 6H), 3.54 (dd, J= 9.8, 4.3 Hz, 1H), 3.46 (dd, J= 9.8, 6.6 Hz, 1H), 1.43 (m, 1H), 1.20 (s, 3H), 1.05 (s, 9H), 1.00 (d, *J* = Hz, 6.6 Hz, 3H) 0.63-0.61 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.3 (C), 135.6 (2C), 129.6 (6CH), 127.6 (4CH), 67.9 (CH_2), 35.6 (CH), 32.0 (C), 26.8 (CH_2), 19.3 (CH), 18.5 (CH_3), 17.1 ($3CH_3$), 14.5 (C), 11.4 (CH_3). HRMS-ESI Calcd for $C_{24}H_{32}O_2$ SiNa $[M+Na]^+$ 403.2069, Found 403.2049. $[\alpha]_D^{25}$ = +27.3 (c 1.1, $CHCl_3$).

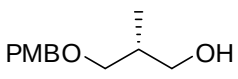
3. Synthesis of the left side aldehyde with PMB as protecting group

(*S*)-Methyl 3-(4-Methoxybenzyloxy)-2-methylpropanoate (8b)



At 0 ºC and under nitrogen atmosphere, PMB-TCA[4] (21.49 g, 76 mmol) was added to a solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (9.4 ml, 83.7 mmol) in dry THF (70 mL). Then triflic acid (0.2ml, 2.28mmol) was added dropwise and the final mixture was stirred for 1.5 h. The reaction was quenched by addition of 50 mL of saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous phase was extracted with Et_2O (2x50 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was eliminated under reduced pressure until the volume was reduced to ¼ of the initial volume. By addition of hexane a white solid was formed, which was filtered through a pad of celite©. The filtrates were concentrated *in vacuo*. The product was purified by column chromatography (9:1 hexane-EtOAc). **8b** (17.92 g, 99%) was obtained as yellow oil. R_f = 0.49 (8:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.20 (m, 2H), 6.89-6.83 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 3.63 (dd, *J* =9.1, 7.3 Hz, 1H), 3.45 (dd, *J* =9.2, 5.9 Hz, 1H), 2.76 (m, 1H), 1.16 (d, *J* =7.1, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.5 (C), 159.7 (C), 129.9 (C), 129.5 (2CH), 115.0 (2CH), 76.6 (CH_2), 73.7 (CH_2), 56.1 (CH_3), 52.6 (CH_3), 41.1 (CH), 13.5 (CH_3). HRMS-ESI Calcd for $C_{13}H_{18}O_4Na$ $[M+Na]^+$ 261.1103, Found 261.1107. $[\alpha]_D^{25}$ = +25.2 (c 1.1, $CHCl_3$).

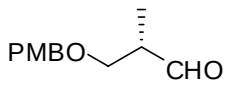
(*R*)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol (22)



4 Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481-1484.

At 0 ºC, a solution of **8b** (10.0 g, 41.86 mmol) in 50 mL of dry THF, was added dropwise to a suspension of $LiAlH_4$ (1.7g, 41.86 mmol) in thf 20 mL of dry THF. After 1 hour 50 mL of Na^+/K^+ tartrate aqueous saturated solution and 20 mL of Et_2O was added and the mixture was stirred until the separation of the phases. The aqueous phase was extracted with 3x20 mL of Et_2O. The combined ethereal phases were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to yield alcohol **22** (7.13 g, 81%) as a yellow oil, which was used in the next step without further purifications. R_f = 0.26 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.20 (m, 2H), 6.91-6.86 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.58 (m, 2H), 3.52 (dd, *J* =9.1, 4.6 Hz, 1H), 3.39 (dd, *J* =8.8, 8.4 Hz, 1H), 2.06 (m, 1H), 0.87 (d, *J* =7.0, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1 (C), 130.0 (C), 19.8 (2CH), 115.1 (2CH), 76.4 (CH_2), 74.5 ($2CH_2$), 67.3 (CH_2), 56.2 (CH_3), 34.8 (CH), 12.7 (CH_3). HRMS-ESI Calcd for $C_{12}H_{18}O_3Na$ $[M+Na]^+$ 233.1154, Found 233.1156. $[\alpha]_D^{25}$ = +13.3 (c 1.1, $CHCl_3$).

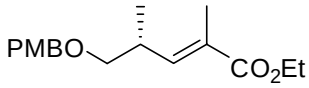
(*S*)-3-(4-Methoxybenzyloxy)-2-methylpropanal (7b)



At −78 ºC and under N_2 atmosphere, $(COCl)_2$ (0.67 mL, 7.72 mmol) is added over 10 mL dry CH_2Cl_2, DMSO (1.09, 15.43 mmol) is then added and the mixture was stirred for 30 min A solution of alcohol **22** (1.01 g, 4.82 mmol) was added in 10 mL of dry CH_2Cl_2 and, after 1 h at this temperature, Et_3N was added dropwise and the solution was allowed to reach room temperature. After completion, 20 mL of water was added, the organic phase was separated and the aqueous one extracted with 2x 10 mL of CH_2Cl_2; the combined organic phases were dried over $MgSO_4$, filtered and the solvent concentrated under reduced pressure to yield the aldehyde **7b** as a yellow oil (0.63 g, 68%). The crude of the reaction was employed in the next step without further purifications); R_f = 0.65 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.70 (d, *J* = 1.6 Hz, 1H), 7.28-7.20 (m, 2H), 6.90-6.86 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.64 (dd, *J* =9.5, 6.7 Hz, 1H), 3.59 (dd, *J* =9.5, 5.6 Hz, 1H), 2.64 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.4 (C), 160.1 (C), 129.9 (C), 129.7 (2CH),

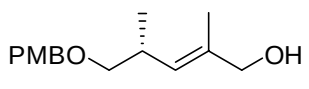
115.1 (2CH), 73.7 (CH_2), 73.1 (CH_2), 56.2 (CH_3), 47.3 (CH), 10.1 (CH_3). HRMS-ESI Calcd for $C_{12}H_{16}O_3Na$ $[M+Na]^+$ 231.0997, Found 231.0997. $[\alpha]_D^{25}$ = +28.3 (c 1.4, $CHCl_3$).

(*R*,*E*)-Ethyl 5-(4-Methoxybenzyloxy)-2,4-dimethylpent-2-enoate (6b)



Aldehyde **7b** (7.30 g, 0.35 mol) was dissolved in 25 mL of CH_2Cl_2, the $Ph_3PC(Me)CO_2Et$ (10.41 g, 0.63 mmol) was added and the reaction was stirred during 16 h at room temperature. The reaction was followed by TLC and after completion 30 mL of saturated aqueous NH_4Cl solution was added. The organic phase was separated and the aqueous one was extracted with 3 x 20 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography to yield **6b** as yellow oil (7.7 g, 76%). R_f = 0.41 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.22 (m, 2H), 6.90-6.85 (m, 2H), 6.57 (dq, *J* =9.7, 1.4 Hz, 1H), 4.44 (s, 2H), 4.18 (q, *J* =7.1 Hz, 2H), 4.26 (dd, *J* =9.4, 6.5 Hz, 1H), 4.20 (dd, *J* =9.5, 5.3 Hz, 1H), 3.80 (s, 3H), 2.83 (m, 1H), 1.86 (d, *J* = 1.3 Hz, 3H), 1.30 (t, *J* =7.1 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2 (C), 160.1 (C), 146.8 (CH), 129.7 (C), 129.7 (2CH), 123.3 (C), 114.8 (2CH), 81.3 (CH_2), 73.7 (CH_2), 62.1 (CH_2), 56.1 (CH_3), 34.6 (CH), 18.3 (CH_3), 14.3 (CH_3), 13.5 (CH_3). HRMS-ESI Calcd for $C_{17}H_{24}O_4Na$ $[M+Na]^+$ 315.1772, Found 315.1773. $[\alpha]_D^{25}$ = +25.0 (c 1.4, $CHCl_3$).

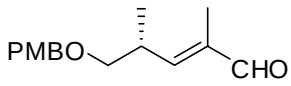
(4*R*,2*E*)-5-(4-Methoxybenzyloxy)-2,4-dimethyl-2-penten-1-ol (5b)



To a solution of ester **6b** (9.30 g, 31.81 mmol) in 45 mL of anhydrous CH_2Cl_2, DIBAL-H 1.0 M in hexanes (6.7 mL, 6.7 mmol) was slowly added at 0 ºC. After 3 h at rt the reaction was completed and the mixture was cooled until 0 ºC. Then 20 mL of

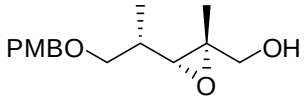
saturated Na^+/K^+ tartrate solution and 20 mL of EtOAc were added. The mixture of the reaction was stirred until complete separation of the phases. The organic phase was separated and the aqueous one extracted with 3 x 20 mL of EtOAc. The combined organic phases were washed with 50 mL NaCl saturated solution, dried over $MgSO_4$, filtered and concentrated. The product was purify by flash chormatography (9:1 hexane:EtOAC) to yield alcohol **5b** as colorless oil (7.01 g, 88%). R_f = 0.25 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.22 (m, 2H), 6.90-6.85 (m, 2H), 5.23 (dq, *J* =9.0, 1.2 Hz, 1H), 4.44 (s, 2H), 3.99 (bs, 2H), 3.80 (s, 3H), 3.30 (dd, *J* =9.1, 6.5 Hz, 1H), 3.24 (dd, *J* =9.2, 7.1 Hz, 1H), 2.73 (m, 1H), 1.68 (d, *J* = 1.3 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8 (C), 132.1 (C), 129.7 (C), 129.5 (2CH), 125.8 (CH), 114.1 (2CH), 81.3 (CH_2), 73.5 (CH_2), 70.1 (CH_2), 55.8 (CH_3), 35.2 (CH), 18.7 (CH_3), 13.6 (CH_3).
HRMS-ESI Calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1467, Found 273.1465. $[\alpha]_D^{25}$ = +21.5 (c 1.2, $CHCl_3$).

(4*R*,2*E*)-5-(4-Methoxybenzyloxy)-2,4-dimethyl-2-pentenal (36)



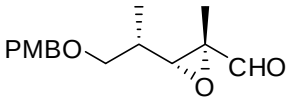
Following the procedure described by Swern, alcohol (**5b**) (1.00 g, 3.99 mmol) was oxidized to aldehyde using $(COCl)_2$ (0.44 mL, 5.99 mmol), DMSO (0.57 mL, 7.99 mmol), Et_3N (2.84 mL, 19.97 mmol), after 1 h the reaction was completed and the work-up was done. The product was purified by flash chromatography (10:1 hexane:EtOAc), to yield aldehyde **36** as a colorless oil (0.74 g, 75%). R_f = 0.63 (7:3 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (s, 1H), 7.24-7.21 (m, 2H), 6.90-6.85 (m, 2H), 5.33 (dq, *J* =9.5, 1.3 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.43 (dd, *J* =9.2, 5.9 Hz, 1H), 3.39 (dd, *J* =9.2, 6.9 Hz, 1H), 3.01 (m, 1H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.4 (C), 159.2 (C), 156.8 (CH), 139.3 (C), 130.2 (2CH), 129.2 (C), 113.8 (2CH), 73.7 (CH_2), 72.8 (CH_2), 55.3 (CH_3), 34.2 (CH), 16.4 (CH_3), 9.4(CH_3). HRMS-ESI Calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1310, Found 271.1302. $[\alpha]_D^{25}$ = +27.2 (c 1.8, $CHCl_3$).

(2*S*,3*R*,4*S*)-2,4-Dimethyl-5-(4-methoxybenzyloxy)-2-oxiranyl-1-pentanol (32)



Following the same procedure described for the synthesis of **34** and using TBHP (0.27 mL, 1.47 mmol), $Ti(O\text{-}iPr)_4$ (0.24 mL, 0.81 mmol) in 25 mL of CH_2Cl_2 was stirred, a solution of allylic alcohol (0.20 g, 0.81 mmol) in 10 mL of CH_2Cl_2. and (-)-DET (0.14 mL, 0.81 mmol). Epoxyalcohol **32** was obtained as yellow oil (0.16 g, 72% yield dr = 10:1). R_f = 0.54 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.64 (m, 2H), 7.40-7.36 (m, 2H), 5.17 (bs, OH), 4.63 (s, 2H), 3.87 (s, 3H), 3.75 (d, *J* = 10.2 Hz, 1H), 3.50 (d, *J* = 9.5 Hz, 1H), 3.46 (dd, *J* = 7.1, 1.3 Hz, 1H), 3.21 (dd, *J* = 7.1, 4.8 Hz, 1H), 2.90 (d, *J* = 9.2 Hz, lH), 1.81 (m, 1H), 1.27 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5 (C), 129.9 (C), 129.7 (2CH), 114.3 (2CH), 76.5 (CH_2), 73.5 (CH_2), 72.5 (CH), 67.3 (CH_2) 59.2 (C), 55.7 (CH_3), 30.3 (CH), 21.1 (CH_3), 15.1 (CH_3). HRMS-ESI Calcd for $C_1H_{22}NaO_4$ $[M+Na]^+$ 289.1416, Found 289.1417.

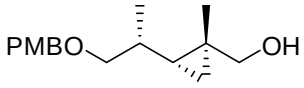
(2*S*,3*R*)-3-[(*S*)-1-(4-Methoxybenzyloxy)propan-2-yl]-2-methyloxirane-2-carbaldehyde (2b)



Following the procedure described by Swern, alcohol **32** (0.15 g, 0.56 mmol) was oxidized to aldehyde using $(COCl)_2$ (78 μL, 0.90 mmol), DMSO (0.13 mL, 1.79 mmol), Et_3N (0.51 mL, 3.64 mmol), after 1 h the reaction was completed and the work-up was done. The product was purified by flash chromatography (8:1 hexane:EtOAc), to yield aldehyde **2b** as a colorless oil (0.13 g, 79%, dr = 10:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (s, 1H), 7.29-7.23 (m, 2H), 6.90-6.86 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.66 (dd, *J* = 10.2, 4.8 Hz, lH), 3.54 (dd, *J* = 10.1, 6.3 Hz, lH), 2.92 (d, *J* = 9.1 Hz, lH),

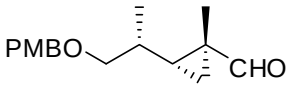
1.92 **(**m**,** lH), 1.14 (d, *J* = 7.1 Hz, 3H), 1.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.9 (C), 159.1 (C), 130.0 (C), 129.0 (2CH), 113.7 (2CH), 76.6 (CH_2), 72.7 (C), 71.6 (CH_2), 63.5 (CH), 55.1 (CH_3), 33.3 (CH), 14.7 (CH_3), 10.7 (CH_3). HRMS-ESI Calcd for $C_{15}H_{20}O_4Na$ $[M+Na]^+$ 287.1259, Found 287.1255. $[\alpha]_D^{25}$ = +12.5 (c 1.1, $CHCl_3$).

{(1*S*,2*R*)-2-[(*R*)-1-(4-Methoxybenzyloxy)propan-2-yl]-1-methylcyclopropyl} methanol (39)



Following the same procedure described for the synthesis of **44**, alcohol **39** was obtained using allylic alcohol **5b** (1.00 g, 4.00 mmol), 1.0 M solution of $ZnEt_2$ in hexanes (7.99 mL, 7.99 mmol) and CH_2I_2, (1.29 mL, 15.98 mmol). The crude of the reaction was chromatographied (8:1 hexane-EtOAc), to yield the hydroxycyclopropane (**39**) as a colorless oil (0.81 g, 77%, dr = 2:1). R_f = 0.35 (7:3 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.64 (m, 2H), 7.40-7.36 (m, 2H), 5.17 (bs, OH), 4.63 (s, 2H), 3.87 (s, 3H), 3.56 (d, *J* = 0.6 Hz, 1H), 3.49 (m, 1H), 3.48 (m, 1H), 3.40 (d, *J* = 0.6 Hz, 1H), 2.63 (m, 1H), 1.03 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.92-0.75 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.7 (C), 129.8 (C), 114.2 (2C), 78.1 (CH_2), 73.3 (CH_2), 71.3 (CH_2), 55.8 (CH_3), 18.2 (C), 17.5 (CH), 17.3 (CH_2), 15.1 (CH_3). HRMS-ESI Calc for $C_{16}H_{24}O_3Na$ $[M+Na]^+$ 287.1623, Found 287.1622. $[\alpha]_D^{25}$ = +25.2 (c 1.0, $CHCl_3$).

(1*S*,2*R*)-2-[(*R*)-1-(4-Methoxybenzyloxy)propan-2-yl]-1-methylcyclopropane carbaldehyde (38)

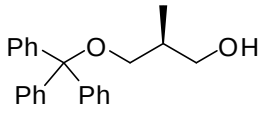


Following the Swern protocol of oxidation, aldehyde **38** was otained using alcohol **39** (0.50 g, 1.89 mmol), $(COCl)_2$ (0.21 mL, 2.84 mmol), DMSO (0.27 mL, 3.78 mmol)and Et_3N (1.34 mL, 9.45 mmol) to yield aldehyde **38** (0.39 mg, 79%). R_f = 0.71

(7:3 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (s, 1H), 7.28-7.23 (m, 2H), 6.88-6.86 (m, 2H), 4.47 (s, 2H), 3.80 (s, 3H), 3.50 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.40 (dd, *J* = 9.1, 6.5 Hz, 1H), 3.33 (dd, *J* = 9.1, 5.06 Hz, 1H), 3.24 (dd, *J* = 9.0, 7.1 Hz, 1H), 2.01 (m, 1H), 1.24 (s, 3H), 1.0 (d, *J* = 6.7 Hz, 3H), 0.98 (m, 1H), 0.76 (dd, *J* = 6.7, 4.8 Hz, 1H), 0.64 (dd, *J* = 6.7, 4.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.0 (C), 159.7 (C), 129.8 (C), 129.6 (2CH), 114.2 (2CH), 77.8 (CH_2), 73.3 (CH_2), 55.8 (CH_3), 40.30 (CH), 31.9 (C), 29.1 (CH_2), 28.2 (CH), 14.8 (CH_3). HRMS-ESI Calcd for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1467, Found 285.1470. $[\alpha]_D^{25}$ = +12.5 (c 1.1, $CHCl_3$).

4. Synthesis of the left side aldehyde with the *Z* double bond

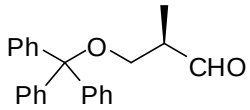
(2*S*)-2-Methyl-3-trityloxy-propan-1-ol (28)



A solution of hydroxyester **(–)-9** (5.68 g, 48.54 mmol) in dry CH_2Cl_2 was stirred at room temperature. TrCl (20.25 g, 72.9 mmol) and Et_3N (10.8 mL, 77.69 mmol) were added, and the mixture was stirred over 16 h. Then a saturated aqueous solution of $NaHCO_3$ was added, the organic phase was separated and after the usual extractive procedure, the combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to yield the protected hydroxyester as a yellow solid. The product was used without further purification in the next step. Over a suspension of $LiAlH_4$ (1.46 g, 38.50 mmol) in 40 ml of dry THF, a solution of the protected hydroxyester in 100 ml of dry THF was added at 0 ºC dropwise. The mixture was heated at 40 ºC during 2 h. Then the solution was cooled until 0 ºC and a saturated aqueous solution of Na^+/K^+ tartrate was added and stirred until complete separation of the phases. The organic was separated and he aqueous extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained as colorless oil (15.86 g, 93% in two steps) and used without further purifications. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, *J* =7.7 Hz, 6H), 7.32 (t, *J*

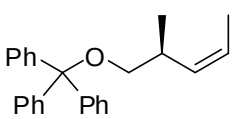
= 7.3 Hz, 6H), 7.26 (t, *J* = 7.2 Hz, 6H), 3.65-3.56 (m, 2H), 3.27 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.07 (dd, *J* = 8.7, 8.0 Hz, 1H), 2.38-2.32 (bs, OH), 2.12-2.02 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.9 (C), 128.6 (CH), 127.8 (CH), 127.0 (CH), 86.9 (CH), 67.7 (CH_2), 67.4 (CH_2), 36.0 (CH), 13.8 (CH_3). HRMS-ESI Calcd for $C_{23}H_{24}O_2Na$ $[M+Na]^+$ 355.1674, Found 355.1674. $[\alpha]_D^{25}$ = –27.0 (c 0.9, $CHCl_3$).

(2*R*)-2-Methyl-3-trityloxy-propanal (29)



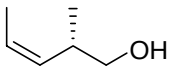
Under N_2 and at −78 ºC, $(COCl)_2$ (9.85 g, 77.63 mmol) was solved in 200 mL of dry CH_2Cl_2, DMSO (7.4 mL, 103.50 mmol) was then added and after 30 min, a solution of alcohol **28** was added dropwise. The mixture was stirred for 1 h and Et_3N (36.0 mL, 258.75 mmol) was added slowly and the reaction was allowed to reach room temperature. The reaction finished after 2.5 h at room temperature. The reaction was quenched with 200 mL of water, the phases were separated and the organic layers were dried over $MgSO_4$ and filtered The solvent was evaporated under reduced pressure to yield the product as yellow oil (42.0 g, 81%) which was used in the next step without further purifications. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (d, *J* = 1.6 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 6H), 7.32 (t, *J* = 7.7 Hz, 6H), 7.26 (t, *J* =7.2 Hz, 3H), 3.42 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.37 (dd, *J* = 9.2, 6.6 Hz, 1H), 2.63 (m, 1H), 1.15 (d, *J* =7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.0 (CH), 143.7 (C), 128.6 (CH), 127.8 (CH), 127.1 (CH), 86.7 (C), 63.6 (CH_2), 44.0 (CH), 10.8 (CH_3). HRMS-ESI Calcd for $C_{23}H_{22}O_2Na$ $[M+Na]^+$ 353.1517, Found 353.1520. $[\alpha]_D^{25}$ = –29.7 (c 0.9, $CHCl_3$).

(2*S*,3*Z*)-2-Methyl-1-trityloxy-3-pentene (30)



Over a suspension of ethyltriphenylphosphoniumbromide (3.20 g, 81.36 mmol) in 100 mL of dry THF at −78°C, BuLi (30.5 mL, 76.30 mmol; 2.50 M in hexane) was slowly added. Afterwards the cooling bath was removed and the orange solution was allowed to reach room temperature. 30 min later, the solution (dark red) was cooled again to –78 ºC and aldehyde **29** (16.80 g , 50.85 mmol) solved in 100 mL of dry THF was slowly added. It was warmed ro room temperature and stirred for 3 h. Afterwards, 200 mL of water were added. The organic phase was separated and the aqueous one was extracted with EtOAc (2x100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. It was further purified by flash chromatography with hexane:EtOAc (10:1) to yield the olefin **30** (15.50 g, 89%) as viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, J = 7.5 Hz, 6H), 7.32 (t, J = 7.7 Hz, 6H), 7.25 (t, J =7.3 Hz, 3H), 5.51 (dq, J =10.9, 6.7 Hz, 1H), 5.25 (ddq, J =10.7, 9.4, 1.5 Hz, 1H), 3.02 (dd, J =8.4, 6.5 Hz, 1H), 2.94 (dd, J =8.3, 7.0 Hz, 1H), 2.82 (m, 1H), 1.69 (dd, J =6.8, 1.5 Hz, 3H), 1.05 (d, J =6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.5 (C), 133.9 (CH), 128.8 (CH), 127.6 (CH), 126.8 (CH), 123.9 (CH), 86.2 (C), 68.1 (CH_2), 32.4 (CH), 17.9 (CH_3), 13.1 (CH_3). HRMS-ESI Calcd for $C_{25}H_{26}ONa$ $[M+Na]^+$ 365.1881, Found 365.1883. $[\alpha]_D^{25}$ = +38.7 (c 1.1, $CHCl_3$).

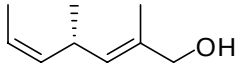
(2*S*,3*Z*)-2-Methyl-3-pentene-1-ol (7a)



To a stirred solution of olefin **30** (14.80 g, 43.22 mmol) in 100 mL of CH_2Cl_2 and 50 mL of MeOH, *p*-toluenesulfonic acid (0.80 g, 4.32 mmol) was added. The reaction was stirred at room temperature during 16 h., then 100 mL of aqueous saturated $NaHCO_3$ solution were added, the organic phase was separated and the aqueous extracted with 2x50 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was distilled at atmosphere pressure (*ca*. 40 ºC), and after, the product was purified by distillation under 1mbar of pressure and trapping the product at -190 ºC. The volatile alcohol **7a** was obtained solved in about 20 mL of CH_2Cl_2 and was used directly in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.61 (dq,

J =11.0, 6.7 Hz, 1H), 5.17 (ddq, *J* =10.9, 9.5, 1.5 Hz, 1H), 3.50 (dd, *J* =10.4, 5.9 Hz, 1H), 3.35 (dd, *J* =10.4, 8.1 Hz, 1H), 2.72 (m, 1H), 1.67 (dd, *J* =6.6, 1.8 Hz, 3H), 1.64 (bs, OH), 0.96 (d, *J* =6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.0 (CH), 126.1 (CH), 67.6 (CH_2), 34.3 (CH), 16.7 (CH_3), 13.1 (CH_2). HRMS-ESI Calcd for $C_6H_{12}ONa$ $[M+Na]^+$ 123.0786, Found 123.0788. $[\alpha]_D^{25}$ = –26.6 (c 1.1, $CHCl_3$).

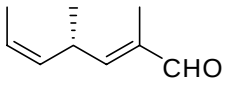
(2*E*,4*S*,5*Z*)-2,4-Dimethyl-hepta-2,5-dien-1-ol (5a)



Oxalyl chloride (8.22 g, 64.80 mmol) was solved in 100 mL of dry CH_2Cl_2 and, at –78 ºC, DMSO (6.1 mL, 86.44 mmol) was added. After 30 min at that temperature, the solution of **7a** in *ca.* 20 mL of CH_2Cl_2 was added. 1h later, still at –78 ºC, Et_3N (21.9 g, 216.0 mmol); was syringed and afterwards it was allowed to reach room temperature. 2h later, Ph_3P=C(Me)CO_2Et (39.1 g, 108.1 mmol) was added to the crude of reaction. It was stirred for 16 h at room temperature and then the reacting mixture was concentrated and redissolved in cold Et_2O. The excess of the yellow precipitated phosporane was filtered and the residue purified by flash chromatography (8:1 hexane:EtOAc) to yield the α,β-unsaturated ester of **7a** as a yellow oil. At –78 ºC and under argon atmosphere, the α,β-unsaturated ester of **7a (**3.44 g, 18.91 mmol) was solved in 50 mL of dry THF and a 1.0 M solution of DIBAL-H in hexanes (47.27 mL, 47.27 mmol) was slowly added. The reaction finished after 2 h at room temperature. Then the mixture was cooled in an ice bath, and 40 mL of a saturated aqueous solution of Na/K tartrate was added. The organic phase was separated and the aqueous was extracted with 3x50 mL of EtOAc. The organic phases were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The product was purified by column chromatography (Hexane/EtOAc, 4:1) to yield the alcohol **5a** as colourless oil (2.12 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.37 (dq, *J* =11.1, 6.6 Hz, 1H), 5.27 (dd, *J* =8.9, 1.1 Hz, 1H), 5.24 (ddq, *J* =10.6 Hz, 9.1, 1.5 Hz, 1H), 3.96 (s, 2H), 3.40 (m, 1H), 1.71 (d, *J* =1.0 Hz, 3H), 1.66 (dd, *J* =6.7, 1.6 Hz, 3H), 1.57 (bs, OH), 1.02 (d, *J* =6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.1 (CH), 133.0 (C), 130.8 (CH), 121.9

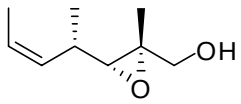
(CH), 68.8 (CH_2), 30.4 (CH), 21.4 (CH_3), 13.7 (CH_3), 12.9 (CH_3). HRMS-ESI Calcd for $C_9H_{16}ONa$ $[M+Na]^+$ 163.1099, Found 163.1101. $[\alpha]_D^{25}$ = +74.2 (c 1.1, $CHCl_3$).

(2*E*,4*S*,5*Z*)-2,4-Dimethylhepta-2,5-dienal (35)



Alcohol **5a (**350 mg, 2.50 mmol) was solved in dry THF and MnO_2 (4.34 g, 50.0 mmol) was added at room temperature. After 1 h the reaction was finished and filtered over Celite which was washed several times with EtOAc. The crude was concentrated under reduced pressure to yield the aldehyde as colorless oil (306 mg, 89%) with enough purity to be used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.36 (s, 1H), 6.31 (dd, *J* =9.5, 1.1 Hz, 1H), 5.49 (dq, *J* =10.7, 6.8 Hz, 1H), 5.31 (ddq, J_1=10.6, 9.0, 1.6 Hz, 1H), 3.66 (m, 1H), 1.79 (d, *J* =1.1 Hz, 3H), 1.65 (dd, *J* =6.8, 1.7 Hz, 3H), 1.14 (d, *J* =6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.4 (CH), 157.8 (CH), 137.0 (C), 132.2 (CH), 124.6 (CH), 31.7 (CH), 20.4 (CH), 13.0 (CH_3), 9.2 (CH_3). HRMS-ESI Calcd for $C_9H_{14}ONa$ $[M+Na]^+$ 161.0942, Found 161.0939. $[\alpha]_D^{25}$ = +120.8 (c 1.1, $CHCl_3$).

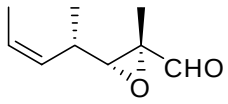
(2*R*,3*R*,4*S*,5*Z*)-2,4-Dimethyl-2-oxiranyl-5-hepten-1-ol (31)



Following the same procedure described for the synthesis of **34** and using TBHP (0.27 mL, 1.47 mmol), Ti(O-iPr)$_4$ (0.24 mL, 0.81 mmol) in 25 mL of CH_2Cl_2 was stirred, a solution of allylic alcohol (114 mg, 0.81 mmol) in 10 mL of CH_2Cl_2. and (-)-DET (0.14 mL, 0.81 mmol). Epoxyalcohol **31** was obtained as yellow oil (57 mg, 45% yield dr = 10:1). R_f = 0.44 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.53 (dq, *J* = 10.6, 6.9 Hz, 1H), 5.21 (ddq, *J* = 10.5, 9.3, 1.6 Hz, 1H), 5.06 (bs, OH), 3.71 (d, *J* = 9.9 Hz, 1H), 3.48 (d, *J* = 9.7 Hz, 1H), 2.73 (m, 1H), 2.54 (d, *J* = 9.0 Hz,

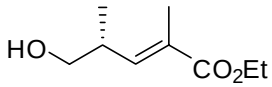
1H), 1.64 (dd, *J* = 6.8, 1.7 Hz, 3H), 1.27 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.1 (CH), 122.1 (CH), 68.6 (CH), 67.9 (CH_2), 58.9 (C), 30.6 (CH), 21.3 (CH_3), 14.3 (CH_3), 12.8 (CH_3). HRMS-ESI Calcd for $C_9H_{16}O_2Na$ $[M+Na]^+$ 179.1048, Found 179.1044. $[\alpha]_D^{25}$ = +64.2 (c 1.3, $CHCl_3$).

(2*S*,3*R*)-2-Methyl-3-[(*S*,*Z*)-pent-3-en-2-yl]oxirane-2-carbaldehyde (2a)



Alcohol **31** (390.6 mg, 2.50 mmol) was solved in dry THF and MnO_2 (4.34 g, 50.0 mmol) was added at room temperature. After 2 h the reaction was finished and filtered over Celite which was washed several times with EtOAc. The crude was concentrated under reduced pressure to yield the aldehyde as colorless oil (300.7 mg, 78%) with enough purity to be used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.53 (s, 1H), 6.36 (dq, *J* = 10.5, 6.7 Hz, 1H), 6.01 (ddq, *J* = 10.3, 9.2, 1.5 Hz, 1H), 3.01 (m, 1H), 2.84 (d, *J* = 9.2 Hz, 1H), 1.81 (dd, *J* = 6.7, 1.6 Hz, 3H), 1.30 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.4 (C), 138.3 (CH), 128.0 (CH), 73.1 (C), 66.3 (CH), 32.2 (CH), 17.9 (CH_3), 14.7 (CH_3), 13.1 (CH_3). HRMS-ESI Calcd for $C_{23}H_{30}O_2SiNa$ $[M+Na]^+$ 389.1913, Found 389.1808. $[\alpha]_D^{25}$ = +72.2 (c 1.4, $CHCl_3$).

(4*R*,2*E*)-Ethyl 5-hydroxy-2,4-dimethyl-2-pentenoate (23)[5]

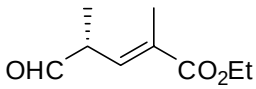


To a stirred solution of the eter **6b** (0.25 g, 0.86mmol) in 5 mL of CH_2Cl_2 and 2 mL of H_2O, DDQ (0.45 g, 1.98 mmol) is added dropwise, the reaction was stirred at r.t. during 4.5 h. Then the reaction was filtered over SiO_2 washing with 20 mL Et_2O. The product (0.13 g, 85%) was used in the next step without futher purifications. R_f = 0.36 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.70 (dq, *J* =9.7, 1.4 Hz, 1H), 4.33

5 Miyazawa, M., Ishibashi, N., Ohnuma, S., Miyashita, M. *Tetrahedron Lett.* **1997**, *38*, 3419-3422.

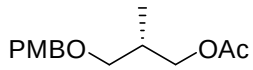
(dd, *J* =9.4, 6.5 Hz, 1H), 4.24 (dd, *J* =9.5, 5.3 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.41 (m, 1H), 1.89 (d, *J* = 1.3 Hz, 3H), 1.30 (t, *J* =7.1 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2 (C), 147.1 (CH), 124.2 (C), 68.5 (CH_2), 61.8 (CH_2), 36.6 (CH), 17.7 (CH_3), 14.2 (CH_3), 13.6 (CH_3). HRMS-ESI Calcd for $C_9H_{16}O_3Na$ $[M+Na]^+$ 195.0997, Found 195.0995. $[\alpha]_D^{25}$ = +13.9 (c 1.2, $CHCl_3$).

(4*R*,2*E*)-Ethyl 2,4-dimethyl-5-oxo-2-pentenoate (24)



At −78 ºC, $(COCl)_2$ (0.10 mL, 1.2 mmol) is added over 5 mL dry CH_2Cl_2, DMSO (0.17 mL, 2.40 mmol) is then added and the mixture was stirred for 30 min A solution of alcohol **23** (125 mg, 0.75 mmol) was added in 5 mL of dry CH_2Cl_2 and, after 1 h at this temperature, Et_3N (0.18 mL, 1.27 mmol) was added dropwise and the solution was allowed to reach room temperature. After 3 h, 10 mL of water was added, the organic phase was separated and the aqueous one extracted with 2x 10 mL of CH_2Cl_2; the combined organic phases were dried over $MgSO_4$, filtered and the solvent concentrated under reduced pressure to yield the aldehyde **24** as a yellow oil (74 mg, 58%); R_f = 0.66 (6:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.68 (d, *J* = 1.6 Hz, 1H), 6.72 (dq, *J* = 9.1, 1.4 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.11 (m, 1H), 2.32 (d, *J* = 1.3 Hz, 3H), 1.30 (t, *J* =7.1 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.7 (CH), 169.3 (C), 146.4 (CH), 127.1 (C), 61.8 (CH_2), 39.6 (CH), 15.7 (CH_3), 14.9 (CH_3), 13.7 (CH_3). HRMS-ESI Calcd for $C_9H_{14}O_3Na$ $[M+Na]^+$ 193.0841, Found 193.0840. $[\alpha]_D^{25}$ = +13.9 (c 1.2, $CHCl_3$).

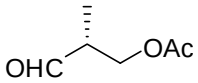
(*2S*)-3-(4-Methoxybenzyloxy)-2-methylpropyl acetate (25)



At room temperature, over a solution of alcohol **22** (125 mg, 0.59 mmol) in 5 mL CH_2Cl_2, Et_3N (0.13 mL, 0.89 mmol), Ac_2O (0.11 mL, 1.18 mmol), and DMAP (7.3

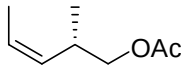
mg, 0.06 mmol) were successively added. The mixture was stirred for 6h, washed with 3 x 10 mL of water and the organic phase was dried over $MgSO_4$, filtered and the solvent concentrated under reduced pressure to yield the acetate **25** as an oil (146 mg, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.23 (m, 2H), 6.88-6.86 (m, 2H), 4.61 (s, 2H), 4.44 (dd, *J* =9.5, 6.7 Hz, 1H), 4.19 (dd, *J* =9.3, 5.0 Hz, 1H), 3.81 (s, 3H), 3.42 (dd, *J* = 7.1, 1.3 Hz, 1H), 3.27 (dd, *J* = 7.2, 4.9 Hz, 1H), 2.63 (m, 1H), 0.95 (d, *J* = 1.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7 (C), 159.1 (C), 130.0 (C), 129.0 (2CH), 113.7 (2CH), 76.6 (CH_2), 72.8 (CH_2), 55.1 (CH_3), 69.1 (CH_2), 31.7 (CH), 20.1 (CH_3), 15.0 (CH_3). HRMS-ESI Calcd for $C_9H_{20}O_4Na$ $[M+Na]^+$ 275.1259, Found 275.1257.

(*R*)-2-Methyl-3-oxopropyl acetate (26)



To a stirred solution of the **25** (215 mg, 0.85 mmol) in 5 mL of CH_2Cl_2, DDQ (231.5 mg, 1.02 mmol) and 2 mL of H_2O were added at 0 ºC. The reaction was completed after 1.5 h at rt, filtered over SiO_2 to remove the excess of DDQ and the byproducts of the reaction, finally the residue was concentrated to dryness, obtaining 63 mg of the corresponding alcohol in 56% yield. At −78 ºC, $(COCl)_2$ (64 μL, 0.77 mmol) is added over 5 mL dry CH_2Cl_2, DMSO (0.11 mL, 1.54 mmol) is then added and the mixture was stirred for 30 min A solution of the alcohol (63 mg, 0.48 mmol) was added in 5 mL of dry CH_2Cl_2 and, after 1 h at this temperature, Et_3N (0.12 mL, 0.81 mmol) was added dropwise and the solution was allowed to reach room temperature. After 3 h, 10 mL of water was added, the organic phase was separated and the aqueous one extracted with 2x 10 mL of CH_2Cl_2; the combined organic phases were dried over $MgSO_4$, filtered and the solvent concentrated under reduced pressure to yield the aldehyde **26** as a yellow oil (45 mg, 72%); R_f = 0.68 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.58 (d, *J* = 2.3 Hz, 1 H), 4.18 (d, *J* =6.1 Hz, 2H), 2.65 (m, 1H), 2.02 (s, 3H), 1.15 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.7 (CH), 171.7 (C), 63.4 (CH_2), 44.7 (CH), 19.9 (CH_3), 10.9 (CH_3). HRMS-ESI Calcd for $C_6H_{10}O_3Na$ $[M+Na]^+$ 153.0528, Found 153.0523.

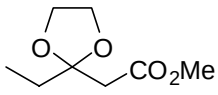
(2*S*,3*Z*)-2-Methyl-3-pentenyl acetate (27)



Over a suspension of ethyltriphenylphosphoniumbromide (0.32 g, 8.14 mmol) in 10 mL of dry THF at −78°C, BuLi (3.1 mL, 7.63 mmol; 2.50 M in hexane) was slowly added. Afterwards the cooling bath was removed and the orange solution was allowed to reach room temperature. 30 min later, the solution (dark red) was cooled again to –78 ºC and aldehyde **26** (0.66 g , 5.09 mmol) solved in 10 mL of dry THF was slowly added. It was warmed ro room temperature and stirred for 3 h. Afterwards, 20 mL of water were added. The organic phase was separated and the aqueous one was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. It was further purified by flash chromatography with hexane:EtOAc (10:1) to yield the olefin **27** (156 mg, 21%) as viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.51 (m, 1H), 5.17 (m, 1H), 3.91 (q, 2H), 3.92 (dd, *J* = 7.1, 1.3 Hz, 1H), 3.77 (dd, *J* = 7.2, 4.9 Hz, 1H), 2.86 (m, 1H), 2.05 (s, 3H), 1.64 (q, 3H), 0.99 (d, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3 (C), 132.3 (CH), 125.4 (CH), 68.8 (CH_2), 31.1 (CH), 21.1 (CH_3), 17.4 (CH_3), 13.2 (CH_3). HRMS-ESI Calcd for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0891, Found 165.0893.

5. Synthesis of the right side aldehyde

Methyl 2-(2-Ethyl-1,3-dioxolan-2-yl)acetate (12)[6]



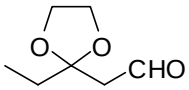
To a stirred solution of methyl 1-acetone carboxylate **13** (9.64 mL, 76.84 mmol) in dry CH_2Cl_2 (250 mL) under nitrogen atmosphere were added ethylene glycol (10.71 mL, 182.10 mmol) and TMSCl (48.68 mL, 425.70). The reaction mixture was then

6 Langer, P.; Freifeld, I. *Synlett* **2001**, *4*, 523-525.

heated under reflux for 48 h and quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. Removal of solvent under reduced pressure afforded **12** (13.18 g, 99%) as a colorless oil. R_f = 0.37 (2:1 hexane-EtOAc). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 4H), 3.69 (s, 6H), 2.67 (s, 2H), 1.82 (q, J = 7.53 Hz, 2H), 0.94 (t, J = 7.53 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0 (C), 109.6 (C), 65.2 ($2CH_2$), 51.7 (CH_3) 42.1 (CH_2), 30.6 (CH2), 7.8 (CH_3).

HRMS-ESI Calcd for $C_9H_{14}O_6Na$ $[M+Na]^+$ 197.0790, Found 197.0799.

2-(2-Ethyl-1,3-dioxolan-2-yl)acetaldehyde (4)[3]



To a suspension of $LiAlH_4$ (2.15 g, 56.74 mmol) in 50 mL of dry THF and at 0 ºC, a solution of ester **12** (13.18 g, 75.76 mmol) in 20 mL of dry THF is added. After the addition, the reaction was heated at 40 ºC during 4 h. The reaction was hydrolyzed with 100 mL of saturated solution of sodium potassium tartrate, and was stirred until the salts were solved. After that, 100 mL of EtOAc is added and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure affording the alcohol with enough purity to oxidize it without further treatments. At −78 ºC, $(COCl)_2$ (7.86 mL, 86.61 mmol) was dissolved in 50 mL of dry CH_2Cl_2, and at the same temperature DMSO (8.19 mL, 115.47 mmol) was added. The solution was stirred during 30 min, and then a solution of the crude alcohol (8.44 g, 57.44 mmol) was added. The mixture was stirred during 1 hour, followed by the addition of Et_3N (41.06 mL, 288.69 mmol) and after 30 more min at −78 ºC, the reaction was allowed to reach room temperature and was finished after 4 h by the addition of 100 mL of saturated aqueous solution of $NaHCO_3$ was added. The phases were separated, the aqueous layer was extracted with 2 x 50 mL of CH_2Cl_2, the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified

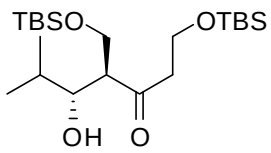
by flash chromatography (3:1 hexane:EtOAc) to yield **4** (8.44 g, 78%) as a yellow oil. R_f = 0.52 (4:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.74 (t, J = 2.95 Hz), 3.94 (s, 4H), 2.68 (d, J = 2.95 Hz, 2H), 1.71 (q, J = 7.40 Hz, 2H), 0.94 (t, J = 7.40 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.6 (C), 109.8 (C), 65.1 ($2CH_2$), 50.2 (CH_2), 31.3 (CH_2), 7.8 (CH_2). HRMS-ESI Calcd for $C_7H_{12}O_3$ $[M+Na]^+$ 144.0786, Found 144.0775.

6. Aldol reaction using Cy_2BCl

General Procedure

Under Ar atmosphere and at -78 ºC, 1.0 M solution of Cy_2BCl in hexanes (1.5 mmol), was diluted with dry Et_2O (0.5 mL). Afterwards, freshly distilled Et_3N (1.7 mmol) and ketone (**3** or 3-pentanone) (1.0 mmol) solved in dry Et_2O (0.5 mL) were sequentially added. The mixture was stirred 45 min at 0 ºC, a white solid appeared, and then the reaction was cooled until −78 ºC when a solution of aldehyde (1.0 mmol) in dry Et_2O (0.5 mL) was added. After 1 h, the reaction was warmed until −20 ºC and stirred during 16 h. MeOH (5mL), pH= 7 buffer (2 mL) and H_2O_2 (2 mL) were added and the mixture stirred for 1 h. The organic phase was separated and the aqueous one extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by flash chromathography (hexane-EtOAc) to yield the aldols as inseparable mixture of diastereomers.

(4*R*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-5-hydroxyl-6-methyl-3-heptanone (45)

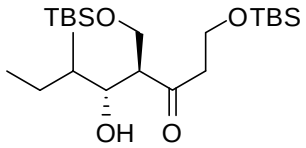


Product **45** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100.0

mg, 0.29 mmol) and aldehyde **46** (26 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **45** (98.4 mg, 81% yield, dr = 7:3) as a colorless oil. R_f = 0.35 (20:1 hexane-EtOAc).

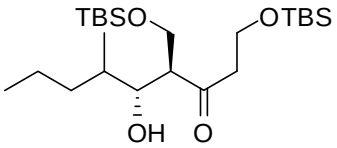
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (t, *J* = 6.6 Hz, 2H), 3.76 (ddd, *J* = 9.7, 8.0, 4.2 Hz, 1H), 3.55 (dd, *J* = 7.8, 4.3 Hz, 1H), 3.45 (dd, *J* = 9.7, 5.2 Hz, 1H), 2.71 (t, *J* = 6.6 Hz, 2H), 2.82 (m, 1H), 1.89 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 6H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 73.1 (CH), 59.2 (CH_2), 58.6 (CH_2), 57.2 (CH), 47.4 (CH_2), 32.2 (CH), 26.1 ($3CH_3$), 25.8 ($3CH_3$), 19.3 ($2CH_3$), 18.2 (C), 18.0 (C), –5.4 ($2CH_3$), –5.8 ($2CH_3$). HRMS-ESI Calcd for $C_{21}H_{46}NaO_4Si_2$ $[M+Na]^+$ 441.2832, Found 441.2832.

(4*R*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-5-hydroxyl-6-methyl-3-octanone (57)



Product **57** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **47** (30 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **57** (94.1 mg, 75% yield) as a colorless oil. R_f = 0.46 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (t, *J* = 6.6 Hz, 2H), 3.75 (dd, *J* = 9.7, 8.0, 4.1 Hz, 1H), 3.55 (dd, *J* = 7.8, 4.3 Hz, 1H), 3.45 (dd, *J* = 9.7, 5.2 Hz, 1H), 2.71 (t, *J* = 6.6 Hz, 2H), 2.83 (m, 1H), 1.87 (m, 1H), 1.55 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 73.1 (CH), 59.2 (CH_2), 58.6 (CH_2), 57.2 (CH), 47.4 (CH_2), 37.2 (CH), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 24.8 (CH_2), 16.8 (CH_3), 18.2 (C), 18.1 (C), 13.6 (CH_3), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{22}H_{48}NaO_4Si_2$ $[M+Na]^+$ 455.2989, Found 455.2991.

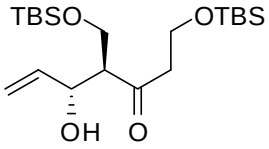
(4*R*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-5-hydroxyl-6-methyl-3- nonanone (58)



Product **58** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **48** (36 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **58** (97.2 mg, 75% yield,) as a yellow oil. R_f = 0.52 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.05 (t, *J* = 6.6 Hz, 2H), 3.77 (dd, *J* = 9.7, 8.0, 4.2 Hz, 1H), 3.54 (dd, *J* = 7.8, 4.3 Hz, 1H), 3.46 (dd, *J* = 9.7, 5.2 Hz, 1H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.81 (m, 1H), 1.88 (m, 1H), 1.32 (m, 2H), 1.25 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 73.1 (CH), 59.2 (CH_2), 58.6 (CH_2), 57.2 (CH), 47.4 (CH_2), 33.8 (CH), 29.9 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 21.8 (CH_2), 18.2 (C), 18.1 (C), 15.1 (CH_3), 13.6 (CH_3), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{23}H_{50}NaO_4Si_2$ $[M+Na]^+$ 469.3145, Found 469.3142.

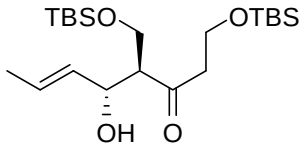
(4*R*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-5-hydroxyl-6-hepten-3-one (59)



Product **59** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **53** (19 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **59** (65.4, 56% yield, dr

= 4:1) as a colorless oil. R_f = 0.45 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (m, 1H), 5.32 (m, 1H), 5.18 (m, 1H), 4.18 (dd, *J* = 7.9, 4.4 Hz, 1H), 3.88 (t, *J* = 6.7 Hz, 2H), 3.69 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.36 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.15 (m, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 138.7 (C), 117.6 (C), 69.1 (CH), 59.2 (CH), 58.6 (CH_2), 57.2 (CH_2), 47.4 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{20}H_{42}O_4NaSi_2$ $[M+Na]^+$ 425.2519, Found 425.2510.

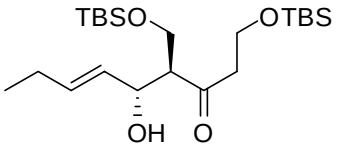
(4*R*,5*S*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-5-hydroxyl-6-octen-3-one (60)



Product **60** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **54** (24 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **60** (76.1 mg, 63% yield, dr = 3:2) as a colorless oil. R_f = 0.43 (20:1 hexane-EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.70-5.68 (m, 2H), 4.18 (dd, *J* = 7.9, 4.3 Hz, 1H), 3.88 (t, *J* = 6.7 Hz, 2H), 3.68 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.32 (dd, *J* = 9.5, 7.9 Hz, 1H), 3.17 (m, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.05 (m, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 132.4 (C), 127.1 (C), 70.1 (CH), 59.1 (CH), 58.6 (CH_2), 57.2 (CH_2), 47.4 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), 17.1 (CH_3), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{21}H_{44}O_4NaSi_2$ $[M+Na]^+$ 439.2676, Found 439.2669.

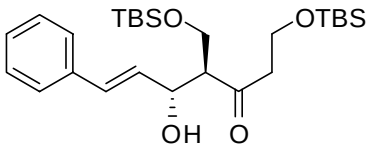
(4*R*,5*S*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxy methyl)-5-hydroxyl-6-nonen-3-one (61)



Product **61** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **55** (28 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **61** (92.4 mg, 74% yield, dr = 7:3) as a colorless oil. R_f = 0.37 (20:1 hexane-EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.70-5.68 (m, 2H), 4.15 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.88 (t, *J* = 6.7 Hz, 2H), 3.68 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.32 (dd, *J* = 9.4, 8.0 Hz, 1H), 3.19 (m, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.05 (m, 2H), 1.08 (t, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 135.7 (C), 130.4 (C), 69.1 (CH), 59.2 (CH), 58.6 (CH_2), 57.2 (CH_2), 47.4 (CH_2), 26.9 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), 14.1 (CH_3), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{22}H_{46}NaO_4Si_2$ $[M+Na]^+$ 453.2832, Found 453.2823.

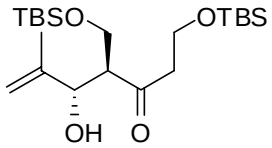
(4*R*,5*S*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxy methyl)-5-hydroxyl-7-phenyl-6-hepten-3-one (62)



Product **62** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **56** (36 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **62** (65.3 mg, 47% yield, dr = 4:1) as a yellow oil. R_f = 0.44 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400

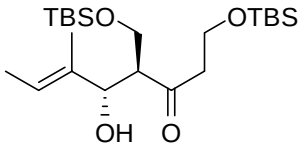
MHz) δ 7.65-7.25 (m, 5H), 6.47 (s, 1H), 6.22 (dd, *J* = 15.8, 7.1 Hz, 1H), 4.18 (dd, *J* = 7.9, 4.5 Hz, 1H), 3.88 (t, *J* = 6.7 Hz, 2H), 3.68 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.35 (dd, *J* = 9.6, 8.0 Hz, 1H), 3.20 (m, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 136.1 (C), 129.2 (CH), 128.7 (2CH), 128.5 (2CH), 127.7 (CH), 126.0 (CH), 68.1 (CH), 59.3 (CH), 58.6 (CH_2), 57.2 (CH_2), 47.4 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{26}H_{46}NaO_4Si_2$ $[M+Na]^+$ 501.2832, Found 501.2820.

(4*R*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxy methyl)-5-hydroxyl-6-methyl-6-hepten-3-one (63)



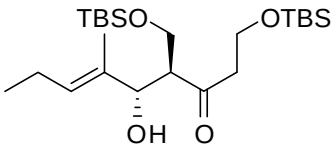
Product **63** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **49** (24 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **63** (96.7 mg, 80% yield, dr = 3:2) as a yellow oil. R_f = 0.51 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.32 (m, 1H), 5.18 (m, 1H), 4.17 (dd, *J* = 7.9, 4.6 Hz, 1H), 3.89 (t, *J* = 6.7 Hz, 2H), 3.68 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.34 (d, *J* = 9.4, 8.0 Hz, 1H), 3.18 (m, 1H), 2.74 (t, *J* = 6.7 Hz, 2H), 1.81 (m, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 143.7 (C), 112.6 (CH_2), 69.8 (CH), 57.2 (CH_2), 56.4 (CH), 56.1 (CH_2), 47.4 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), 17.2 (CH_3), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{21}H_{41}NaO_4Si_2$ $[M+Na]^+$ 439.2676, Found 439.2674.

(4*R*,5*S*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxy methyl)-5-hydroxyl-6-methyl-6-octen-3-one (64)



Product **64** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **50** (28 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **64** (81.2 mg, 65% yield, dr = 7:3) as a colorless oil. R_f = 0.42 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.42 (m, 1H), 4.18 (dd, *J* = 7.9, 4.5 Hz, 1H), 3.88 (t, *J* = 6.7 Hz, 2H), 3.68 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.36 (d, *J* = 9.6, 8.0 Hz, 1H), 3.16 (m, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.52 (m, 3H), 1.82 (m, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 138.7 (C), 119.6 (CH_2), 70.7 (CH), 57.1 (CH_2), 56.4 (CH), 56.2 (CH_2), 47.5 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), 13.5 (CH_3), 12.1 (CH_3),–5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{22}H_{46}NaO_4Si_2$ $[M+Na]^+$ 453.2832, Found 453.2832.

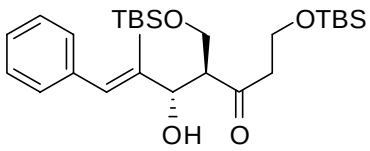
(4*R*,5*S*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxy methyl)-5-hydroxyl-6-methyl-6-nonen-3-one (65)



Product **65** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **51** (33 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **65** (100.6 mg, 78% yield, dr = 4:1) as a yellow oil. R_f = 0.38 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400

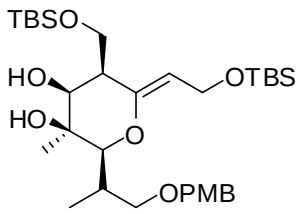
MHz) δ 5.42 (m, 1H), 4.16 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.88 (t, *J* = 6.7 Hz, 2H), 3.68 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.35 (d, *J* = 9.4, 8.0 Hz, 1H), 3.17 (m, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.48 (m, 2H), 1.81 (m, 3H), 1.08 (t, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 135.5 (C), 121.6 (CH_2), 72.0 (CH), 57.1 (CH_2), 56.4 (CH), 56.2 (CH_2), 47.7 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 22.1 (CH_2), 18.2 (C), 18.1 (C), 15.0 (CH_3), 12.4 (CH_3),–5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{23}H_{48}NaO_4Si_2$ $[M+Na]^+$ 467.2989, Found 467.2989.

(4*R*,5*S*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxy methyl)-5-hydroxyl-6-methyl-7-phenyl-6-hepten-3-one (66)



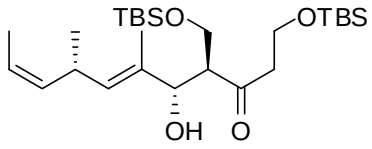
Product **66** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **52 (**40 μL, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield **66** (61.5 mg, 43% yield, dr = 7:3) as a yellow oil. R_f = 0.41 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65-7.25 (m, 5H), 6.45 (s, 1H), 4.17 (dd, *J* = 7.9, 4.3 Hz, 1H), 3.88 (t, *J* = 6.7 Hz, 2H), 3.68 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.37 (d, *J* = 9.5, 8.0 Hz, 1H), 3.14 (m, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 1.80 (m, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7 (C), 136.3 (C), 135.3 (C), 128.6 (2CH), 128.5 (2CH), 127.7 (CH), 127.6 (CH), 123.9 (CH), 70.5 (CH), 57.3 (CH_2), 56.9 (CH), 56.1 (CH_2), 47.1 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), 13.8 (CH_3), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{27}H_{48}NaO_4Si_2$ $[M+Na]^+$ 515.2989, Found 515.2992.

(2*R*,3*R*,4*R*,5*S*)-6-{(*E*)-2-[(*tert*-Butyldimethilsilyl)oxy]ethyliden}-5-{[(*tert*-butyldimethyilsilyl)oxy]methyl}-3-methyl-2-{(1*R*)-1-methyl-2-[(4-methoxybencyl)oxy]ethyl}-3,4,5,6-tetrahydro-2H-pyran-3,4-diol (67)



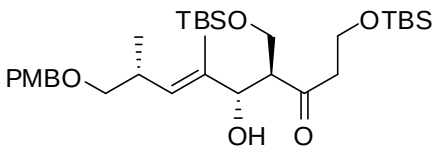
Product **67** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **2b** (77 mg, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (20:1 hexane-EtOAc) to yield the pirane **67** (0.12 g, 65% yield) as a colorless oil. R_f = 0.46 (20:1 hexane-EtOAc^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.27 (m, 2H), 6.90-6.87 (m, 2H), 4.48 (s, 2H), 4.35 (td, *J* = 7.1, 2.0 Hz, 1H), 4.28 (dd, *J* = 7.4, 1.5 Hz, 1H), 4.27 (d, *J* = 2.1 Hz, 1H), 4.21 (dd, *J* = 6.0, 1.5 Hz, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 3.94 (dd, *J* = 9.3, 8.9 Hz, 1H), 3.81 (s, 3H), 3.68 (dd, *J* = 9.5, 4.9 Hz, 1H), 3.51 (dd, *J* = 7.0, 6.7 Hz, 1H) 3.28 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.14 (m, 1H), 2.05 (m, 1H), 1.17 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.80 (d, *J* = 6.0 Hz, 3H), 0.09 (s, 6H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2 (C), 152.3 (C), 130.5 (C), 129.2 (2CH), 113.8 (2CH), 98.3 (CH), 83.9 (C), 73.8 (CH), 73.6 (CH), 72.9 (CH_2), 72.8 (CH_2), 59.4 (CH_2), 58.0 (CH_2), 55.3 (CH_3), 50.0 (CH), 35.2 (CH), 26.1 ($3CH_3$), 25.9 ($3CH_3$), 20.9 (CH_3), 18.4 (C), 18.3 (C), 9.7(CH_3), -5.0 (CH_3), -5.1 (CH_3), -5.4 (CH_3), -5.4 (CH_3). HRMS-ESI Calcd for $C_{32}H_{58}O_7Si_2Na$ $[M+Na]^+$ 633.3619, Found 633.3626.). The structure was confirmed by 2D-NMR techniques (HSQC, HMBC, ROESY, COSY).

(4*R*,5*S*,6*E*,8*S*,9*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-{[(*tert*-butyldimethyl silyl)oxy]methyl}-5-hydroxy-6,8-dimethylundeca-6,9-dien-3-one (70)



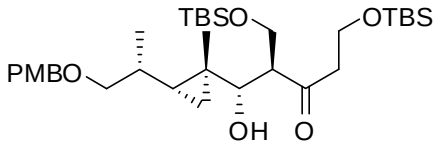
Product **70** was synthesized following the general procedure described above using Cy_2BCl (0.22 mL, 0.22 mmol), Et_3N (35 µL, 0.25 mmol), ketone **3b** (50 mg, 0.15 mmol) and aldehyde **35** (40 mg, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (20:1 hexane-EtOAc) to yield the aldol **70** (51 mg, 72% yield) as a colorless oil. R_f = 0.46 (20:1 hexane-EtOAc). Spectroscopic data are referred to the major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.34 (dq, *J* =11.1, 6.6 Hz, 1H), 5.23 (d, *J* = 8.9 Hz, 1H), 5.14 (ddd, *J* = 10.6 Hz, 9.1, 1.5 Hz, 1H), 4.15 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.86 (t, *J* = 6.8 Hz, 2H), 3.68 (dd, *J* = 9.7, 8.3 Hz, 1H), 3.39 (dd, *J* = 9.5, 8.0 Hz, 1H), 3.37 (m, 1H), 3.16 (m, 1H), 2.74 (t, *J* = 6.7 Hz, 3H), 1.69 (d, *J* = 1.0 Hz, 3H), 1.66 (dd, *J* = 6.7, 1.6 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.2 (C), 135.2 (CH), 132.8 (C), 130.9 (CH), 122.9 (CH), 73.6 (CH), 62.4 (CH_2), 58.4 (CH_2), 57.2 (CH), 47.9 (CH_2), 30.5 (CH), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 21.6 (CH_3), 17.4 (C), 17.3 (C), 13.3 (CH_3), 12.5 (CH_3), -5.6 ($2CH_3$), -5.6 ($2CH_3$). HRMS-ESI Calcd for $C_{26}H_{52}O_4Si_2Na$ $[M+Na]^+$ 507.3302, Found 507.3300. The structure was confirmed by 2D-NMR techniques (HSQC, COSY).

(4*R*,5*S*,6*E*,8*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-{[(*tert*-butyldimethylsilyl)oxy]methyl}-5-hydroxy-6,8-dimethyl-9-(4-methoxybenzyl)non-6-en-3-one (71)



Product **71** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **36** (72.0 mg, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (20:1 hexane-EtOAc) to yield the aldol **71** (172 mg, 81% yield) as a colorless oil. R_f = 0.46 (20:1 hexane-EtOAc). Spectroscopic data are referred to the major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.22 (m, 2H), 6.89-6.84 (m, 2H), 5.21 (dq, *J* = 8.9, 1.1 Hz, 1H), 4.42 (s, 2H), 4.22 (d, *J* = 8.5 Hz, 1H), 3.90 (t, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 3.70 (dd, *J* = 9.8, 8.2 Hz, 1H), 3.59 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.29 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.23 (dd, *J* = 9.1, 7.4 Hz, 1H), 3.00 (m, 1H), 2.76 (t, *J* = 6.8, 2H), 2.71 (m, 1H), 1.66 (s, 3H), 0.96 (d, *J* = 6.7, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.2 (C), 153.1 (C), 134.9 (C), 129.9 (C), 129.0 (2CH), 125.2 (CH), 113.7 (2CH), 74.7 (CH_2), 72.6 (CH_2), 72.3 (CH), 58.4 (CH_2), 57.3 (CH), 55.9 (CH_3), 55.3 (CH_2), 47.9 (CH_2), 32.8 (CH), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 19.2 (CH_3), 18.1 (2C), 11.8 (CH_3), -5.6 ($2CH_3$), -5.6 ($2CH_3$). HRMS-ESI Calcd for $C_{32}H_{58}O_6Si_2Na$ $[M+Na]^+$ 617.3670, Found 617.3672. The structure was confirmed by 2D-NMR techniques (HSQC, COSY).

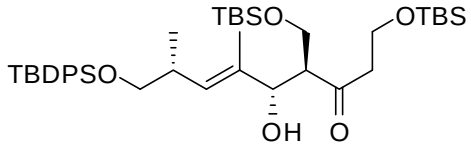
(1*S*,2*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1-hydroxy-1-[(1*S*,2*R*)-1-methyl-2-{(1*R*)-1-methyl-2-[(4-methoxybenzyl)oxy]ethyl}cyclopropyl]pentan-3-one (91)



91 was synthesized following the general procedure described above using Cy_2BCl (0.17 mL, 0.17 mmol), Et_3N (28 µL, 0.19 mmol), ketone **3b** (40 mg, 0.12 mmol) and aldehyde **38** (76.0 mg, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (20:1 hexane-EtOAc) to yield the **91** (43 mg, 61% yield) as a colorless oil. R_f = 0.46 (20:1 hexane-EtOAc). Spectroscopic data are referred to the major isomer^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.22 (m, 2H), 6.89-6.84 (m, 2H), 4.01 (t, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.70 (dd, *J* = 9.8, 8.2 Hz, 1H), 3.61 (d, *J* =

8.6 Hz, 1H), 3.59 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.56 (d, *J* = 0.6 Hz, 1H), 3.49 (m, 1H), 3.48 (m, 1H), 3.40 (d, *J* = 0.6 Hz, 1H), 2.73 (t, *J* = 6.6, 3H), 2.63 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.92-0.75 (m, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.1 (C), 159.7 (C), 129.8 (C), 114.2 (2C), 78.1 (CH_2), 73.3 (CH_2), 70.2 (CH), 58.3 (CH_2), 56.3 (CH), 55.8 (CH_3), 55.4 (CH_2), 47.8 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 17.5 (CH), 17.3 (CH_2), 17.1 (2C), 15.1 (CH_3), -5.6 ($2CH_3$), -5.6 ($2CH_3$). HRMS-ESI Calcd for $C_{33}H_{60}O_6Si_2Na$ $[M+Na]^+$ 631.3826, Found 631.3822. The structure was confirmed by 2D-NMR techniques (HSQC, COSY).

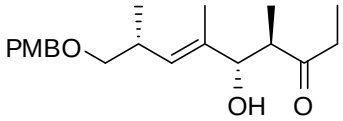
(2*S*, 3*E*, 5*S*, 6*R*)-9-(*tert*-Butyldimethylsilyloxy)-6-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-2,4-dimethyl-non-3-en-7-one (72)



Product **72** was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **3b** (100 mg, 0.29 mmol) and aldehyde **37** (106 mg, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (20:1 hexane-EtOAc) to yield the aldol **72** (184 mg, 89% yield) as a colorless oil. R_f = 0.36 (15:1 hexane-EtOAc). Spectroscopic data are referred to the major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63-7.60 (m, 4H), 7.46-7.33 (m, 6H), 5.15 (d, *J* = 9.8 Hz, 1H), 4.17 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.88 (t, *J* = 6.7 Hz, 2H), 3.66 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.51 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.48 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.37 (dd, *J* = 9.6, 8.0 Hz, 1H), 2.96 (td, *J* = 7.9, 5.1 Hz, 1H), 2.73 (t, *J* = 6.6, 2H), 2.67 (d, *J* = 4.1, 1H), 2.59 (m, 1H), 1.55 (s, 3H), 1.04 (s, 9H), 1.01 (d, *J* = 6.6, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.8 (C), 135.7 (2C), 135.6 (4CH), 135.1 (C), 130.7 (2CH), 129.6 (4CH), 127.6 (CH), 76.1 (CH), 68.2 (CH_2), 62.6 (CH_2), 58.4 (CH_2), 57.2 (CH), 48.0 (CH_2), 35.2 (CH_3), 26.9 ($3CH_3$), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 19.3 (C), 18.2 (C), 18.1 (C), 17.3 (CH_3), 11.9 (CH_3), -5.4 ($2CH_3$), -5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{40}H_{68}O_5Si_3Na$

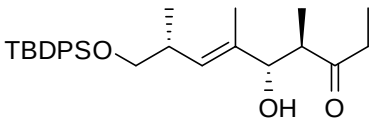
$[M+Na]^+$ 735.4272, Found 735.4272. The structure was confirmed by 2D-NMR techniques (HSQC, COSY).

(4*R*,5*S*,6*E*,8*R*)-5-Hydroxy-4,6,8-trimethyl-9-(4-methoxybenzyl)non-6-en-3-one (83)



83 was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **80** (86.1 mg, 0.29 mmol) and aldehyde **36** (72 mg, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield the **83** (88.3 mg, 91% yield) as a colorless oil. R_f = 0.46 (4:1 hexane-EtOAc). Spectroscopic data are referred to the major isomer. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.22 (m, 2H), 6.89-6.84 (m, 2H), 5.21 (d, *J* = 8.7 Hz, 1H), 4.41 (s, 2H), 4.12 (d, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 3.25 (d, *J* = 6.9 Hz, 2H), 2.89-2.62 (m, 2H), 2.54 (m, 2H), 1.62 (s, 3H), 1.03 (t, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.6 (C), 159.1 (C), 134.8 (C), 132.4 (CH), 130.5 (C), 129.1 (2CH), 113.7 (2CH), 80.2 (CH_2), 74.9 (CH), 72.6 (CH_2), 55.3 (CH_3), 48.6 (CH), 36.4 (CH), 32.8 (CH_2), 20.5 (CH_3), 14.2 (CH_3), 11.2 (CH_3), 7.4 (CH_3). HRMS-ESI Calcd for $C_{20}H_{30}NaO_4$ $[M+Na]^+$ 357.2042, Found 357.2043. The structure was confirmed by 2D-NMR techniques (HSQC, COSY).

(3*E*,4*R*,5*S*,8*R*)-9-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-4,6,8-trimethylnon-6-en-3-one (84)



84 was synthesized following the general procedure described above using Cy_2BCl (0.43 mL, 0.43 mmol), Et_3N (0.07 mL, 0.49 mmol), ketone **80** (86.1 mg, 0.29

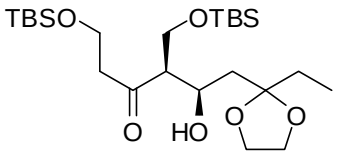
mmol) and aldehyde **37** (106 mg, 0.29 mmol) in 1.5 mL Et_2O. The product was purified by flash chromatography (10:1 hexane-EtOAc) to yield the **84** (124.7 mg, 95% yield) as a colorless oil. R_f = 0.46 (4:1 hexane-EtOAc). Spectroscopic data are referred to the major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69-7.61 (m, 4H), 7.45-7.33 (m, 6H), 5.15 (d, *J* = 9.7 Hz, 1H), 3.59 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.54 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.43 (d, *J* = 6.7, 1H), 3.20 (m, 1H), 2.56 (m, 1H), 2.43 (q, *J* = 6.6 Hz, 2H), 1.71 (d, *J* =1.0 Hz, 3H), 1.19 (d, *J* =6.6 Hz, 3H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 1.01 (3, *J* =6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.8 (C), 135.7 (2C), 135.6 (4CH), 135.1 (C), 130.7 (2CH), 129.6 (4CH), 127.6 (CH), 74.9 (CH), 48.6 (CH), 36.9 (CH), 32.8 (CH_2), 25.9 ($3CH_3$), 20.5 (CH_3), 19.3 (C), 14.2 (CH_3), 11.2 (CH_3), 7.4 (CH_3). HRMS-ESI Calcd for $C_{28}H_{40}NaO_3Si$ $[M+Na]^+$ 475.2644, Found 475.2644. The structure was confirmed by 2D-NMR techniques (HSQC, COSY).

7. Aldol reaction using $TiCl_4$

General Procedure

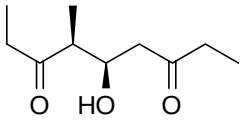
To a stirred solution of ketone (1.00 mmol) in 0.5 mL of CH_2Cl_2, 1.20 mmol of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 was added. After 10 min at 0 ºC, DIPEA (1.40 mmol) was added at −78 ºC. The mixture was stirred during 15 min at −78 ºC, and a solution of aldehyde (1.10 mmol) in 0.5 mL of CH_2Cl_2 was added. The reaction was stirred during 4 h at the same temperature and 10 mL of saturated solution of NH_4Cl were added. The organic phase was separated and the aqueous one extracted with 2 x 10 mL of CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was purified by flash chromatography (hexane-EtOAc) to yield the aldols as inseparable mixture of diastereomers.

(4*S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-[2-(*tert*-butyldimethyl silyloxy) ethyl]-7-(1,3-dioxolan-2-yl)-5-hydroxylundecan-3-one (78)



Following the general procedure described above, using ketone **3b** (345 mg, 1.00 mmol), $TiCl_4$ (1.20 mL, 1.20 mmol), DIPEA (0.24 mL, 1.40 mmol) and aldehyde **4** (159 mg, 1.10 mmol); aldol **78** (335 mg, 68% yield) was obtained as a colorless oil. R_f = 0.46 (4:1 hexane-EtOAc). Spectroscopic data are referred to the major isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.01 (m, 2H), 3.97 (m, 2H), 3.86 (t, *J* = 6.7 Hz, 2H), 3.66 (dd, *J* = 9.9, 7.9 Hz, 1H), 3.57 (m, 1H), 3.37 (dd, *J* = 9.6, 7.9 Hz, 1H), 2.71 (t, *J* = 6.6, 2H), 2.59 (m, 1H), 1.89 (m, 2H), 1.67 (q, *J* = 7.5 Hz, 2H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.8 (C), 112.7 (C), 64.8 ($2CH_2$), 60.1 (CH), 62.6 (CH_2), 58.9 (CH_2), 58.4 (CH_2), 54.6 (CH), 48.0 (CH_2), 37.6 (CH_2), 29.8 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), 8.1 (CH_3), -5.4 ($2CH_3$), -5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{24}H_{50}NaO_6Si_2$ $[M+Na]^+$ 513.3044, Found 513.3044. The structure was confirmed by 2D-NMR techniques (HSQC, COSY).

(4*S*,5*R*)-5-Hydroxy-4-methylnonane-3,7-dione (88)



Following the general procedure described above, ketone **80** (86.13 mg, 1.00 mmol), $TiCl_4$ (1.20 mL, 1.20 mmol), DIPEA (0.24 mL, 1.40 mmol) and aldehyde **4** (159 mg, 1.10 mmol); **88** (143.4 mg, 77% yield) was obtained as a colorless oil. R_f = 0.46 (4:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.31 (dt, *J* = 9.0, 4.7 Hz, 1H), 2.72 (dq, *J* = 9.0, 7.2 Hz, 1H), 2.51 (d, *J* = 4.7 Hz, 2H), 2.46 (q, *J* = 7.3 Hz, 4H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$,

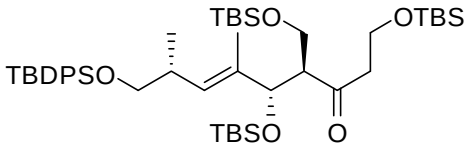
100 MHz) δ 215.1 (C), 211.7 (C), 68.2 (CH), 49.7 (CH), 45.5 (CH_2), 36.8 (CH_2), 35.7 (CH_2), 11.6 (CH_3), 7.5 (CH_3), 7.5 (CH_3). HRMS-ESI Calcd for $C_{10}H_{18}O_3Na$ $[M+Na]^+$ 209.1154, Found 209.1154.

8. Hydroxyl protection of aldol products

General Procedure

To a stirred solution of 0.18 mmol of the aldol in 5 mL of CH_2Cl_2, 0.26 mmol of TBSOTf and 0.35 mmol of 2,6-lutidine were sequentially added at 0 ºC. The reaction was stirred at this temperature for 30 min and then, saturated solution of NH_4Cl.was added. The organic phase was separated, and after extraction of the aqueous layer with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The product was purified by flash chromatography (30:1 hexane:EtOAc) to yield the protected aldol.

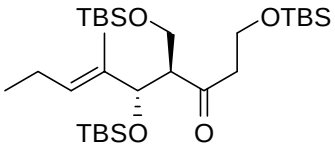
(4*R*,5*S*,6*E*,8*R*)-9-[(*tert*-Butyldimethylsilyl)oxy]-1,5-bis[(*tert*-butyldimethylsilyl)oxy]-4-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6,8-dimethylnon-6-en-3-one (74)



Following the general procedure described above, using aldol **72** (128.4 mg, 0.18 mmol), of TBSOTf (60 µL, 0.26 mmol), 2,6-lutidine (41 µL , 0.35 mmol); TBS-protected aldol **74** (143.0 mg, 96% yield) was obtained as a colorless oil. R_f = 0.39 (30:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64-7.60 (m, 4H), 7.47-7.33 (m, 6H), 5.13 (d, *J* = 9.8 Hz, 1H), 4.27 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.86 (t, *J* = 6.7 Hz, 2H), 3.55 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.51 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.48 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.43 (dd, *J* = 9.6, 8.0 Hz, 1H), 3.11 (td, *J* = 7.9, 5.1 Hz, 1H), 2.74 (t, *J* = 6.6, 2H), 2.59 (m, 1H), 1.53 (s, 3H), 1.04 (s, 9H), 1.00 (d, *J* = 6.6, 3H), 0.95 (s, 9H), 0.88 (s,

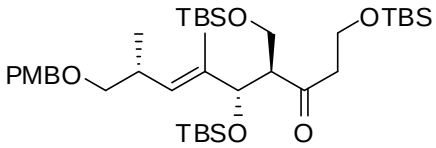
9H), 0.84 (s, 9H), 0.07 (s, 6H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.7 (C), 135.7 (2C), 135.6 (4CH), 135.1 (C), 130.7 (2CH), 129.6 (4CH), 127.6 (CH), 77.4 (CH), 63.2 (CH_2), 61.6 (CH_2), 58.2 (CH_2), 57.0 (CH), 48.0 (CH_2), 35.2 (CH_3), 25.9 ($3CH_3$), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 19.3 (C), 18.2 (C), 18.1 (C), 18.1 (C), 17.3 (CH_3), 11.9 (CH_3), –5.2 ($2CH_3$), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{46}H_{82}O5Si_4Na$ $[M+Na]^+$ 849.5137, Found 849.5140.

(3*E*,5*S*,6*R*)-5,9-Di(*tert*-butyldimethylsilyloxy)-6-[2-(*tert*-butyldimethyl silyloxy) ethyl]-4-methyl-3-nonen-7-one (75)



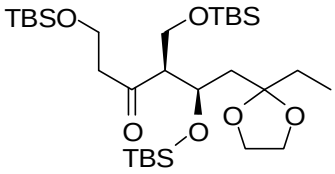
Following the general procedure described above, using aldol **65** (80.1 mg, 0.18 mmol), of TBSOTf (60 µL, 0.26 mmol), 2,6-lutidine (41 µL, 0.35 mmol); TBS-protected aldol **75** (97.6 mg, 97% yield) was obtained as a colorless oil. R_f = 0.24 (30:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.40 (m, 1H), 4.25 (dd, J = 7.9, 4.1 Hz, 1H), 3.86 (t, J = 6.7 Hz, 2H), 3.62 (dd, J = 9.9, 8.0 Hz, 1H), 3.41 (d, J = 9.4, 8.0 Hz, 1H), 3.31 (m, 1H), 2.72 (t, J = 6.7 Hz, 2H), 2.49 (m, 2H), 1.80 (m, 3H), 1.09 (t, J = 6.5 Hz, 3H), 0.95 (s, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.07 (s, 6H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.1 (C), 135.7 (C), 121.3 (CH_2), 76.0 (CH), 56.9 (CH_2), 56.3 (CH), 56.2 (CH_2), 47.7 (CH_2), 30.0 ($3CH_3$), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 25.8 ($3CH_3$), 22.1 (CH_2), 18.2 (C), 18.1 (C), 18.1 (C), 15.3 (CH_3), 12.4 (CH_3), –5.3 ($2CH_3$), –5.4 ($2CH_3$), –5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{29}H_{62}O_4Si_3Na$ $[M+Na]^+$ 581.3854, Found 581.3856.

(2*S*,3*E*,5*S*,6*R*)-5,9-Di(*tert*-butyldimethylsilyloxy)-6-[2-(*tert*-butyldimethylsilyloxy) ethyl]-1-(4-methoxybenzyloxy)-2,4-dimethyl-non-3-en-7-one (73)



Following the general procedure described above, using aldol **71** (107.1 mg, 0.18 mmol), of TBSOTf (60 µL, 0.26 mmol), 2,6-lutidine (41 µL , 0.35 mmol); TBS-protected aldol **73** (125.1 mg, 98% yield) was obtained as a colorless oil. R_f = 0.34 (30:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.22 (m, 2H), 6.89-6.83 (m, 2H), 5.19 (dq, *J* = 8.9, 1.1 Hz, 1H), 4.42 (s, 2H), 4.31 (d, *J* = 8.7 Hz, 1H), 3.86 (t, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 3.61 (dd, *J* = 9.8, 8.2 Hz, 1H), 3.59 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.38 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.23 (dd, *J* = 9.1, 7.4 Hz, 1H), 3.16 (m, 1H), 2.75 (t, *J* = 6.9 Hz, 2H), 2.71 (m, 1H), 1.63 (s, 3H), 0.95 (d, *J* = 6.7, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.3 (C), 152.6 (C), 134.4 (C), 129.9 (C), 129.0 (2CH), 125.2 (CH), 113.7 (2CH), 76.1 (CH_2), 72.7 (CH_2), 72.0 (CH), 58.4 (CH_2), 57.6 (CH), 55.9 (CH_3), 55.3 (CH_2), 48.1 (CH_2), 32.8 (CH), 25.9 ($3CH_3$), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 19.5 (CH_3), 18.1 (2C), 18.0 (C), 11.8 (CH_3), -5.5 ($2CH_3$), -5.6 ($2CH_3$), -5.6 ($2CH_3$). HRMS-ESI Calcd for $C_{38}H_{72}O_6Si_3Na$ $[M+Na]^+$ 731.4534, Found 731.4538.

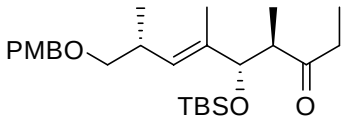
(4*S*,5*R*)-1,5-Di(*tert*-butyldimethylsilyloxy)-4-[2-(*tert*-butyldimethyl silyloxy) ethyl]-7-(1,3-dioxolan-2-yl)undecan-3-one (77)



Following the general procedure described above, using aldol **78** (88.3 mg, 0.18 mmol), of TBSOTf (60 µL, 0.26 mmol), 2,6-lutidine (41 µL, 0.35 mmol); TBS-protected aldol **77** (143.4 mg, 77% yield) was obtained as a colorless oil. R_f = 0.31

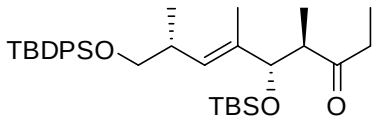
(30:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.00 (m, 2H), 3.96 (m, 2H), 3.84 (t, J = 6.7 Hz, 2H), 3.59 (dd, J = 9.9, 7.9 Hz, 1H), 3.69 (m, 1H), 3.46 (dd, J = 9.6, 7.9 Hz, 1H), 2.70 (t, J = 6.6 Hz, 2H), 2.72 (m, 1H), 1.96 (m, 2H), 1.68 (q, J = 7.5 Hz, 2H), 0.96 (s, 9H), 0.92 (t, J = 7.5 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.07 (s, 6H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.9 (C), 113.4 (C), 64.1 ($2CH_2$), 60.3 (CH), 62.5 (CH_2), 58.9 (CH_2), 58.7 (CH_2), 55.0 (CH), 48.1 (CH_2), 37.6 (CH_2), 29.9 (CH_2), 25.9 ($3CH_3$), 25.8 ($3CH_3$), 25.8 ($3CH_3$), 18.2 (C), 18.1 (C), 18.1 (C), 8.1 (CH_3), -5.4 ($2CH_3$), -5.5 ($2CH_3$), -5.7 ($2CH_3$). HRMS-ESI Calcd for $C_{30}H_{64}O_6Si_3Na$ $[M+Na]^+$ 627.3908, Found 627.3904.

(4*R*,5*S*,8*R*,*E*)-5-(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-4,6,8-trimethylnon-6-en-3-one (85)



Following the general procedure described above, using aldol **83** (88.3 mg, 0.264 mmol), of TBSOTf (88 µL, 0.383 mmol), 2,6-lutidine (60 µL , 0.516 mmol); TBS-protected aldol **85** (116.1 mg, 98% yield) was obtained as a colorless oil. R_f = 0.31 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.22 (m, 2H), 6.89-6.83 (m, 2H), 5.20 (d, J = 8.7 Hz, 1H), 4.41 (s, 2H), 4.27 (d, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.23 (d, J = 6.9 Hz, 2H), 2.88-2.61 (m, 2H), 2.54 (m, 2H), 1.62 (s, 3H), 1.03 (t, J = 6.7 Hz, 3H), 0.97 (d, J = 6.0 Hz, 3H), 0.94 (d, J = 6.1 Hz, 3H), 0.92 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.4 (C), 159.6 (C), 133.5 (C), 129.4 (C), 129.2 (2CH), 125.2 (CH), 114.4 (2CH), 81.1 (CH_2), 77.5 (CH), 73.0 (CH_2), 55.6 (CH_3), 49.6 (CH), 35.2 (CH), 34.9 (CH_2), 29.9 ($3CH_3$), 18.5 (C), 18.1 (CH_3), 12.8 (CH_3), 10.7 (CH_3), 8.2 (CH_3) -5.5 ($2CH_3$). HRMS-ESI Calcd for $C_{26}H_{44}O_4SiNa$ $[M+Na]^+$ 448.3009, Found 448.3008.

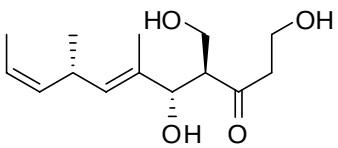
(4*R*,5*S*,8*R*,*E*)-5-(tert-butyldimethylsilyloxy)-9-(tert-butyldiphenylsilyloxy)-4,6,8-trimethylnon-6-en-3-one (86)



Following the general procedure described above, using aldol **84** (122.4 mg, 0.270 mmol), of TBSOTf (90 µL, 0.392 mmol), 2,6-lutidine (62 µL, 0.527 mmol); TBS-protected aldol **86** (151.5 mg, 99% yield) was obtained as a colorless oil. R_f = 0.35 (20:1 hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69-7.61 (m, 4H), 7.45-7.33 (m, 6H), 5.14 (d, *J* = 10.1 Hz, 1H), 4.32 (d, *J* = 7.8 Hz, 1H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.63 (dd, *J* = 9.9, 8.2 Hz, 1H), 3.48 (dq, *J* = 15.7, 4.9 Hz, 1H), 3.35 (dd, *J* = 9.6, 7.9 Hz, 1H), 2.97 (td, *J* = 7.8, 5.0 Hz, 1H), 2.73 (t, *J* = 6.6, 2H), 2.67 (d, *J* = 4.8, 1H), 2.59 (m, 1H), δ 1.04 (s, 9H), 1.01 (d, *J* = 6.6, 3H), 1.55 (s, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.6 (C), 135.8 (2C), 135.6 (4CH), 133.3 (C), 130.7 (2CH), 129.6 (4CH), 125.1 (CH), 77.3 (CH), 70.5 (CH_2), 49.5 (CH), 38.2 (CH), 34.9 (CH_2), 27.3 ($3CH_3$), 25.8 ($3CH_3$), 19.0 (C), 18.2 (C), 18.1 (CH_2), 12.8 (CH_3), 10.7 (CH_3), 8.2 (CH_3) -5.5 ($2CH_3$). HRMS-ESI Calcd for $C_{34}H_{54}O_3Si_2Na$ $[M+Na]^+$ 566.3611, Found 566.3613.

9. Deprotection for activity assays

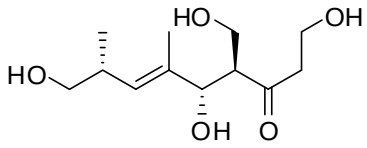
(4*R*,5*S*,6*E*,8*S*,9*Z*)-1,5-dihydroxy-4-(hydroxymethyl)-6,8-dimethylundeca-6,9-dien-3-one (92)



To a solution of the silyl ether **70** (15 mg, 0.031 mmol) in 1.0 mL of THF, 1.0 M solution of TBAF in THF (125 µL, 0.125 mmol) was added at 0 ºC. The reaction was

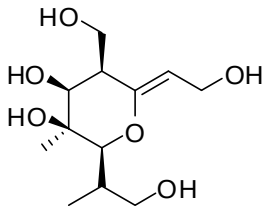
allowed to reach rt and stirred for 2 h. The reaction was followed by TLC until completion. 2 mL of aqueous saturated solution of NH_4Cl was added, the phases were separated and the aqueous layer was extracted with 2 x 5 mL of CH_2Cl_2. The combined organic phases were concentrated. The crude was redissolved in 10 mL of 1:1 CH_2Cl_2-MeOH and filtered through a pad of celite. The crude was employed to measure the biological activity without further purifications. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.35 (dq, *J* =11.1, 6.6 Hz, 1H), 5.22 (d, *J* = 8.9 Hz, 1H), 5.15 (ddd, *J* = 10.6 Hz, 9.1, 1.6 Hz, 1H), 4.28 (dd, *J* = 9.7, 3.9 Hz, 1H), 3.99 (t, *J* = 6.8 Hz, 2H), 3.82 (dd, *J* = 9.7, 8.3 Hz, 1H), 3.41 (d, *J* = 9.5, 1H), 3.35 (m, 1H), 3.13 (m, 1H), 2.71 (t, *J* = 6.7 Hz, 3H), 1.70 (d, *J* =1.1 Hz, 3H), 1.67 (dd, *J* = 6.7, 1.6 Hz, 3H), 1.03 (d, *J* =6.7 Hz, 3H).

(4*R*,5*S*,8*R*,*E*)-1,5,9-trihydroxy-4-(hydroxymethyl)-6,8-dimethylnon-6-en-3-one (93)



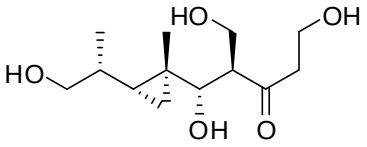
To a solution of the silyl ether **72** (18 mg, 0.025 mmol) in 1.5 mL of THF, 1.0 M solution of TBAF in THF (150 µL, 0.150 mmol) was added at 0 ºC. The reaction was allowed to reach rt and stirred for 2 h. The reaction was followed by TLC until completion. 2 mL of aqueous saturated solution of NH_4Cl was added, the phases were separated and the aqueous layer was extracted with 2 x 5 mL of CH_2Cl_2. The combined organic phases were concentrated. The crude was redissolved in 10 mL of 1:1 CH_2Cl_2-MeOH and filtered through a pad of celite. The crude was employed to measure the biological activity without further purifications. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.20 (d, *J* = 8.7 Hz, 1H), 4.28 (d, *J* = 9.7, 3.9 Hz, 1H), 3.99 (t, *J* = 6.8 Hz, 2H), 3.82 (dd, *J* = 9.7, 8.3 Hz, 1H), 3.55 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.51 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.41 (d, *J* = 9.5, 8.1 Hz, 1H), 3.35 (m, 1H), 2.71 (t, *J* = 6.7 Hz, 3H), 2.59 (m, 1H), 1.66 (d, *J* =1.0 Hz, 3H), 1.19 (d, *J* =6.7 Hz, 3H).

(2*S*,3*S*,4*S*,5*R*,*Z*)-6-(2-hydroxyethylidene)-5-(hydroxymethyl)-2-((S)-1-hydroxypropan-2-yl)-3-methyltetrahydro-2H-pyran-3,4-diol (94)



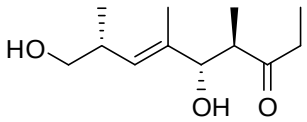
To a solution of **67** (20 mg, 0.0327 mmol) in 1.5 mL of THF, 1.0 M solution of TBAF in THF (131 µL, 0.131 mmol) was added at 0 ºC. The reaction was allowed to reach rt and stirred for 2 h. The reaction was followed by TLC until completion. 2 mL of aqueous saturated solution of NH_4Cl was added, the phases were separated and the aqueous layer was extracted with 2 x 5 mL of CH_2Cl_2. The combined organic phases were concentrated. The crude was redissolved in 10 mL of 1:1 CH_2Cl_2-MeOH and filtered through a pad of celite. After solvent evaporation, the crude was redissolved in 2 mL of 1:1 mixture of CH_2Cl_2-H_2O and DDQ (8.1 mg, 0.0360) was added at rt The reaction was stirred at rt for 1h, filtered through a pad of celite and employed to measure the biological activity without further purifications. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.39 (s, 2H), 4.31 (td, *J* = 7.3, 1.9 Hz, 1H), 4.15 (dd, *J* = 7.4, 1.7 Hz, 1H), 4.12 (d, *J* = 2.2 Hz, 1H), 4.06 (dd, *J* = 6.0, 1.4 Hz, 1H), 4.01 (d, *J* = 3.7 Hz, 1H), 3.95 (dd, *J* = 9.3, 8.8 Hz, 1H), 3.69 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.48 (dd, *J* = 7.2, 6.7 Hz, 1H) 3.26 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.13 (m, 1H), 2.07 (m, 1H), 1.15 (s, 3H), 0.80 (d, *J* = 6.0 Hz, 3H).

(1*S*,2*R*)-1,5-dihydroxy-2-(hydroxymethyl)-1-((1*S*,2*R*)-2-((*R*)-1-hydroxypropan-2-yl)-1-methylcyclopropyl)pentan-3-one (95)



To a solution of **91** (15 mg, 0.0246 mmol) in 1.5 mL of THF, 1.0 M solution of TBAF in THF (100 µL, 0.100 mmol) was added at 0 ºC. The reaction was allowed to reach rt and stirred for 2 h. The reaction was followed by TLC until completion. 2 mL of aqueous saturated solution of NH_4Cl was added, the phases were separated and the aqueous layer was extracted with 2 x 5 mL of CH_2Cl_2. The combined organic phases were concentrated. The crude was redissolved in 10 mL of 1:1 CH_2Cl_2-MeOH and filtered through a pad of celite. After solvent evaporation, the crude was redissolved in 2 mL of 1:1 mixture of CH_2Cl_2-H_2O and DDQ (6.1 mg, 0.0271 mmol) was added at rt The reaction was stirred at rt for 1h, filtered through a pad of celite and employed to measure the biological activity without further purifications. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (t, *J* = 7.0 Hz, 2H), 3.78 (dd, *J* = 9.9, 8.2 Hz, 1H), 3.69 (d, *J* = 8.6 Hz, 1H), 3.54 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.51 (d, *J* = 0.7 Hz, 1H), 3.43 (m, 1H), 3.40 (m, 1H), 3.37 (d, *J* = 0.6 Hz, 1H), 2.68 (t, *J* = 6.7, 3H), 2.55 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.92-0.75 (m, 3H).

(4*R*,5*S*,8*R*,*E*)-5,9-dihydroxy-4,6,8-trimethylnon-6-en-3-one (96)



To a solution of the silyl ether **84** (18 mg, 0.0398 mmol) in 1.0 mL of THF, 1.0 M solution of TBAF in THF (80 µL, 0.0800 mmol) was added at 0 ºC. The reaction was allowed to reach rt and stirred for 2 h. The reaction was followed by TLC until completion. 2 mL of aqueous saturated solution of NH_4Cl was added, the phases were separated and the aqueous layer was extracted with 2 x 5 mL of CH_2Cl_2. The combined organic phases were concentrated. The crude was redissolved in 10 mL of 1:1 CH_2Cl_2-MeOH and filtered through a pad of celite. The crude was employed to measure the biological activity without further purifications. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.20 (d, *J* = 8.7 Hz, 1H), 3.55 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.51 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.41 (d, *J* = 9.5, 1H), 3.21 (m, 1H), 2.59 (m, 1H), 2.43 (q, *J* = 6.6 Hz, 2H), 1.71 (d, *J* =1.0 Hz, 3H), 1.19 (d, *J* =6.6 Hz, 3H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.03 (3, *J* =6.7 Hz, 3H).

10. Cytotoxicity assay protocol

Cell lines and cell culture

Human-derived established cell lines used in this study were purchased from ATCC (American Type Culture Collection) unless otherwise specified.

A-549, human lung carcinoma
HT-29, human colorectal adenocarcinoma
MDA-MB 231, human breast adenocarcinoma

All cell lines are maintained in RPMI medium culture supplemented with 10% Fetal calf serum (FCS), 2 mM L-glutamine and 100 Units/mL penicillin and streptomycin at 37 ºC and 5% CO_2. Triplicate cultures were incubated for 72 h in the presence or absence of test compounds (at 10 concentrations ranging from 10 to 0.0026 µg/mL).

Cytotoxicity assay (srb)

A colorimetric assay using sulforhodamine B (SRB) has been adapted for a quantitative measurement of cell growth and viability, following a previously described method.[7] Cells are plated in 96-well microtiter plates at a density of $5x10^3$/well and incubated for 24 h. After that, cells are treated with vehicle alone (control) or compounds at the concentrations indicated. One plate from each different cell line is fixed and stained, and used for Tz reference (see next paragraph). Treated cells are further incubated for 48 h. To quantify the cytotoxic potential of compounds the sulforhodamine B (SRB) protein stain method is used.

7 Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Waren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. New colorimetric cytotoxicity assay for anticancer drug screening, *J. Natl. Cancer Inst*., **1990**, *82*, 1107-1112.

Cells are washed twice with phosphate buffered saline (PBS), fixed for 15 min in 1% glutaraldehyde solution, rinsed twice in PBS, and stained in 0.4% SRB solution for 30 min at room temperature. Cells are then rinsed several times in 1% acetic acid solution and air-dried. SRB was then extracted in 10 mM trizma base solution and the absorbance measured at 490 nm. Cell survival was determined as percentage of control cell growth.